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Second Class

Effective cholesterol control

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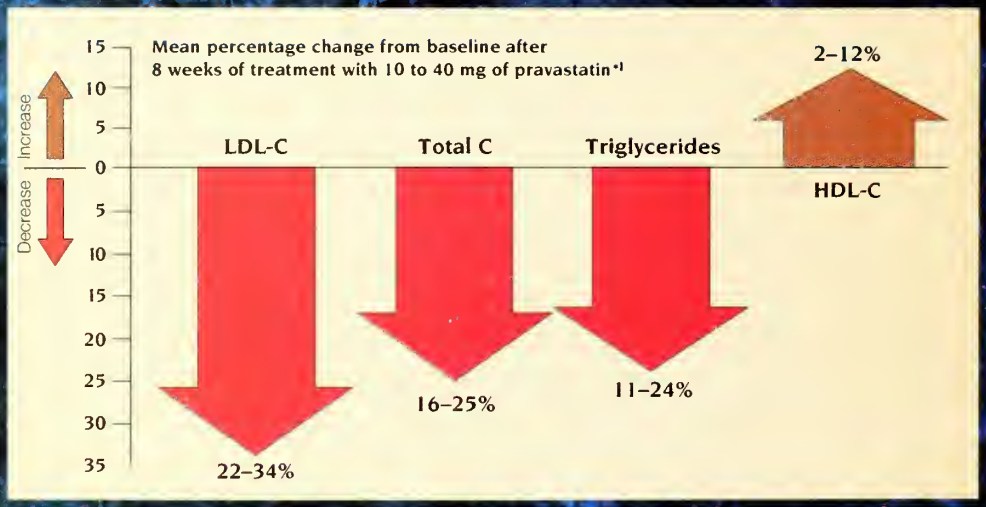

*Each arrow represents a range of means derived from a single placebo-controlled study that included 55 patients treated with pravastatin.

PRAVACHOL® (pravastatin sodium) is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease *or* unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin.

Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

PRAVACHOL™
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Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

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PRAVACHOL® (Pravastatin Sodium Tablets)

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of child-bearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient appnsed of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin.* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol: Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Hardenan gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells; and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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INSTRUCTIONS FOR AUTHORS

Our readership represents all specialties of medicine. We wish to receive and publish manuscripts that are valid, important, lively, well-written, and succinct. They should be of interest to a broad range of busy practitioners, students, researchers, and scholars who have a clinical orientation. The purpose of a paper or letter may be to alert, review, discuss—above all, to teach. Titles should be short and intriguing. Avoid jargon, the overuse of abbreviations and acronyms, sexist language, redundancies, or expendable words and phrases (see *AMA Manual of Style,* 8th Edition).

Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine,* 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, this should be noted in the cover letter and a copy of that publication should be included.

Manuscripts should not exceed 3,000 words (15 double-spaced pages). Case Reports, Alerts, and Notices should not exceed 1,500 words. Lessons From the Practice should not exceed 1,000 words.

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include a nonstructured abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor **must be double-spaced** and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent galley proofs before publication.

All manuscripts will be subject to peer review to determine the originality, validity, and importance of content and conclusions. Reviewers' comments will be returned with rejected manuscripts at the discretion of the Editors. All reviewers will remain anonymous. Any conflict of interest, actual or potential, should be revealed to the Editors (see Letter of Transmittal).

All accepted manuscripts are subject to copyediting, and the corresponding author is sent edited galley proofs for approval and necessary minor changes. Excessive changes at this stage may result in a delay of publication or withdrawal of the paper. No changes will be made after the final, edited version has been approved by the corresponding author without notifying the author. It is the corresponding author's responsibility to clear all corrections and changes with his or her coauthors.

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The letter of transmittal must include a statement of financial disclosure: "I warrant that I have no financial interest in the drugs, devices, or procedures described in the enclosed manuscript (except as disclosed in the attached statement)."

Research or project support should be included as a footnote to the manuscript or in the accompanying cover letter.

Manuscripts concerned with experimental investigation on human subjects must include in the text a statement that all subjects gave their informed consent and that approval of the appropriate ethics committee was obtained.

Acknowledgments

Acknowledgments will be printed on a select basis—to acknowledge those who contributed to but were not involved in the writing or review of the paper. They should not include persons whose work on the manuscript was a part of their regular duties.

Preparation of Manuscripts

Everything, including references, tables, figure legends, and abstracts, **must be double-spaced.**

The original manuscript and two copies should be submitted on standard-sized heavy bond paper. Allow a margin of 2.5 to 4 cm (1 to 1.5 in) on both sides. Manuscripts transmitted by facsimile machine are not acceptable unless requested by the Editors.

All values should be in Système International (SI) units, with metric equivalents following in parentheses. Temperature readings should be given in Celsius. Use the generic name of drugs, with the salt or ester given when first used.

Figures (illustrations) should be submitted in triplicate in black and white, unmounted 12.7 × 17.8 cm (5 × 7 in) glossy prints, with the figure number, author's name, and top of the photo indicated with a label on the back. Patients (and

relatives) have a right to anonymity in published clinical documentation. Details that might identify patients should be avoided unless essential for scientific purposes. Masking of the eye region in photographs of patients may be inadequate protection of anonymity. If identification of patients is unavoidable, informed consent should be obtained, and this should be clearly stated in the article. Changing data on patients should not be used as a way of securing anonymity. Figure legends, to be typed in sequence on the same page, should be in complete sentences. Any figures or tables previously published must be accompanied by a letter of permission to borrow from the copyright holder (the previous publisher). The permission of the authors should also be obtained. The Editors discourage the use of borrowed figures or tables.

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References

All references should be cited in the text using superscript numbers and listed in their order of citation. They should be pertinent to the text and not simply a listing of the results of a computerized search. They should be in *WJM* style per the examples given below.

(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

Journal Articles

Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

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(T. Harris, "Selenium-Rich Sediments Also Have Been Reported in Wildlife Refuges," *The Sacramento Bee*, September 8, 1985, p 5)

Personal Communications and Unpublished Data

This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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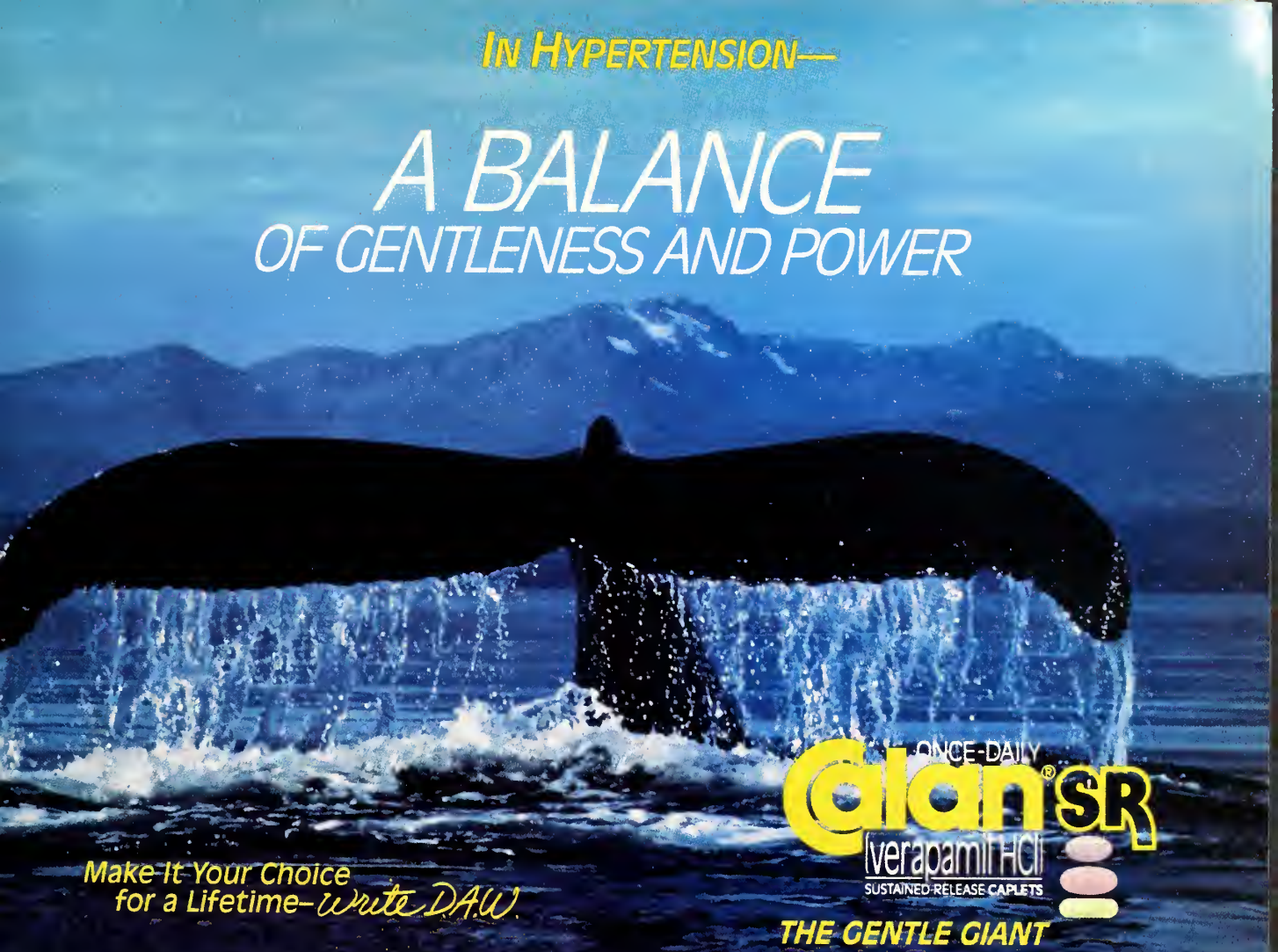
IN HYPERTENSION—

A BALANCE
OF GENTLENESS AND POWER



The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Pracautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainida and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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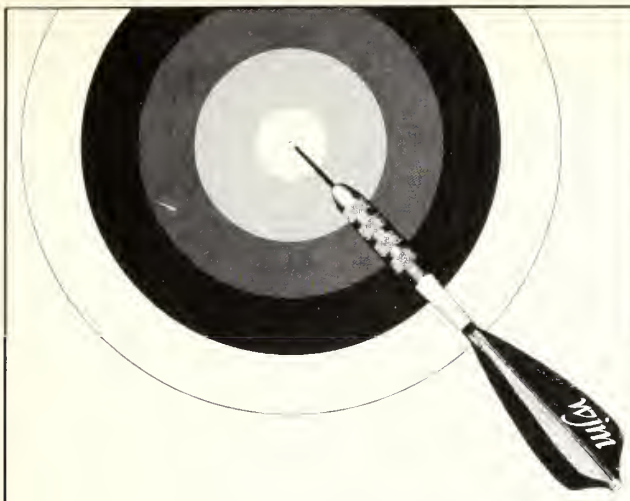

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★ Official Journal of the Alaska State Medical Association, the Arizona Medical Association, the California Medical Association, the Denver Medical Society, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah Medical Association, the Washington State Medical Association, and the Wyoming Medical Society.

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From Depression...Into the Mainstream

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BRIEF SUMMARY

ZOLOFT™ (sertraline HCl)

INDICATIONS AND USAGE: ZOLOFT (sertraline hydrochloride) is indicated for the treatment of depression.

CONTRAINDICATIONS: None known. **WARNINGS: In patients receiving another serotonin reuptake inhibitor drug in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, it is recommended that ZOLOFT (sertraline hydrochloride) not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping ZOLOFT before starting an MAOI.** **PRECAUTIONS** ***General:*** **Activation of Mania/Hypomania** - During premarketing testing, hypomania or mania occurred in approximately 0.4% of ZOLOFT (sertraline hydrochloride) treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with Major Affective Disorder treated with other marketed antidepressants. **Weight Loss** - Significant weight loss may be an undesirable result of treatment with sertraline for some patients, but on average, patients in controlled trials had minimal, 1 to 2 pound weight loss, versus smaller changes on placebo. Only rarely have sertraline patients been discontinued for weight loss. **Seizure** - ZOLOFT has not been evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarket testing. Accordingly, like other antidepressants, ZOLOFT should be introduced with care in epileptic patients. **Suicide** - The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high risk patients should accompany initial drug therapy. Prescriptions for ZOLOFT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Weak Uricosuric Effect** - ZOLOFT is associated with a mean decrease in serum uric acid of approximately 7%. The clinical significance of this weak uricosuric effect is unknown, and there have been no reports of acute renal failure with ZOLOFT. **Use in Patients with Concomitant Illness** - Clinical experience with ZOLOFT in patients with certain concomitant systemic illness is limited. Caution is advisable in using ZOLOFT in patients with diseases or conditions that could affect metabolism or hemodynamic responses. ZOLOFT has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during the product's premarket testing. However, the electrocardiograms of 774 patients who received ZOLOFT in double-blind trials were evaluated and the data indicate that ZOLOFT is not associated with the development of significant ECG abnormalities. ZOLOFT is extensively metabolized by the liver. The pharmacokinetics of ZOLOFT have not been studied in patients with significant hepatic dysfunction nor have patients with significant hepatic dysfunction been evaluated during treatment with ZOLOFT. Accordingly, ZOLOFT should be used with caution in such patients. Since ZOLOFT is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until the pharmacokinetics of ZOLOFT have been studied in patients with renal impairment and until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with ZOLOFT, it should be used with caution in such patients. **Interference with Cognitive and Motor Performance** - In controlled studies, ZOLOFT did not cause sedation and did not interfere with psychomotor performance. ***Information for Patients:*** Physicians are advised to discuss the following issues with patients for whom they prescribe ZOLOFT. Patients should be told that although ZOLOFT has not been shown to impair the ability of normal subjects to perform tasks requiring complex motor and mental skills in laboratory experiments, drugs that act upon the central nervous system may affect some individuals adversely. Patients should be told that although ZOLOFT has not been shown in experiments with normal subjects to increase the mental and motor skill impairments caused by alcohol, the concomitant use of ZOLOFT and alcohol in depressed patients is not advised. Patients should be told that while no adverse interaction of ZOLOFT with over-the-counter (OTC) drug products is known to occur, the potential for interaction exists. Thus, the use of any OTC product should be initiated cautiously according to the directions of use given for the OTC product. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physician if they are breast-feeding an infant. ***Laboratory Tests:*** None. ***Drug Interactions:*** **Potential Effects of Coadministration of Drugs Highly Bound to Plasma Proteins** - Because sertraline is tightly bound to plasma protein, the administration of ZOLOFT (sertraline hydrochloride) to a patient taking another drug which is tightly bound to protein (e.g., warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein-bound ZOLOFT by other tightly bound drugs. In a study comparing prothrombin time AUC (0-120 hr) following dosing with warfarin (0.75 mg/kg) before and after 21 days of dosing with either ZOLOFT (50-200 mg/day) or placebo, there was a mean increase in prothrombin time of 8% relative to baseline for ZOLOFT compared to a 1% decrease for placebo ($p<0.02$). The normalization of prothrombin time for the ZOLOFT group was delayed compared to the placebo group. The clinical significance of this change is unknown. Accordingly, prothrombin time should be carefully monitored when ZOLOFT therapy is initiated or stopped. **CNS Active Drugs** - In a study comparing the disposition of intravenously administered diazepam before and after 21 days of dosing with either ZOLOFT (50 to 200 mg/day escalating dose) or placebo, there was a 32% decrease relative to baseline in diazepam clearance for the ZOLOFT group compared to a 19% decrease relative to baseline for the placebo group ($p<0.03$). There was a 23% increase in T_{max} for desmethyldiazepam in the ZOLOFT group compared to a 20% decrease in the placebo group ($p<0.03$). The clinical significance of these changes is unknown. In a placebo-controlled trial in normal volunteers, the administration of two doses of ZOLOFT did not significantly alter steady-state lithium levels or the renal clearance of lithium. Nonetheless, at this time, it is recommended that plasma lithium levels be monitored following initiation of ZOLOFT therapy with appropriate adjustments to the lithium dose. The risk of using ZOLOFT in combination with other CNS active drugs has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of ZOLOFT and such drugs is required. **Hypoglycemic Drugs** - In a placebo-controlled trial in normal volunteers, administration of ZOLOFT for 22 days (including 200 mg/day for the final 13 days) caused a statistically significant 16% decrease from baseline in the clearance of tolbutamide following an intravenous 1000 mg dose. ZOLOFT administration did not noticeably change either the plasma protein binding or the apparent volume of distribution of tolbutamide, suggesting that the decreased clearance was due to a change in the metabolism of the drug. The clinical significance of this decrease in tolbutamide clearance is unknown. **Atenolol** - ZOLOFT (100 mg) when administered to 10 healthy male subjects had no effect on the beta-adrenergic blocking ability of atenolol. **Microsomal Enzyme Induction** - Preclinical studies have shown ZOLOFT to induce hepatic microsomal enzymes. In clinical studies ZOLOFT was shown to induce hepatic enzymes minimally as determined by a small (5%) but statistically significant decrease in antipyrine half-life following administration of 200 mg/day for 21 days. This small change in antipyrine half-life reflects a clinically insignificant change in hepatic metabolism. **Electroconvulsive Therapy** - There are no clinical studies establishing the risks or benefits of the combined use of electroconvulsive therapy (ECT) and ZOLOFT. **Alcohol** - Although ZOLOFT did not potentiate the cognitive and psychomotor effects of alcohol in experiments with normal subjects, the concomitant use of ZOLOFT and alcohol in depressed patients is not recommended. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were carried out in CD-1 mice and Long-Evans rats at doses up to 40 mg/kg in mice (10 times on a mg/kg basis and the same on a mg/m² basis as the maximum recommended human dose) and at doses up to 40 mg/kg in rats (10 times on a mg/kg basis and 2 times on a mg/m² basis, the maximum recommended human dose). There was a dose-related increase in the incidence of liver adenomas in male mice receiving sertraline at 10-40 mg/kg. No increase was seen in female mice or in rats of either sex receiving the same treatments, nor was there an increase in hepatocellular carcinomas. Liver adenomas have a variable rate of spontaneous occurrence in the CD-1 mouse and are of unknown significance to humans. There was an increase in follicular adenomas of the thyroid in female rats receiving sertraline at 40 mg/kg; this was not accompanied by thyroid hyperplasia. While there was an increase in uterine adenocarcinomas in rats receiving sertraline at 10-40 mg/kg compared to placebo controls, this effect was not clearly drug related. Sertraline had no genotoxic effects, with or without metabolic activation, based on the following assays: bacterial mutation assay; mouse lymphoma mutation assay; and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes. A decrease in fertility was seen in one of two rat studies at a dose of 80 mg/kg (20 times the maximum human dose on a mg/kg basis and 4 times on a mg/m² basis). ***Pregnancy—Pregnancy Category B:*** **Teratogenic Effects** - Reproduction studies have been performed in rats and rabbits at doses up to approximately 20 times and 10 times the maximum daily human mg/kg dose (4 to 4.5 times the mg/m² dose), respectively. There was no evidence of teratogenicity at any dose level. At doses approximately 2.5-10 times the maximum daily human mg/kg dose, sertraline was associated with delayed ossification in fetuses, probably secondary to effects on the dams. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Non-teratogenic Effects** - There was also decreased neonatal survival following maternal administration of sertraline at doses as low as approximately 5 times the maximum human mg/kg dose. The decrease in pup survival was shown to be most probably due to *in utero* exposure to sertraline. The clinical significance of these effects is unknown. **Labor and Delivery** - The effect of ZOLOFT on labor and delivery in humans is unknown. **Nursing Mothers** - It is not known whether, and if so in what amount, sertraline or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ZOLOFT is administered to a nursing woman. **Pediatric Use** - Safety and effectiveness in children have not been established. **Geriatric Use** - Several hundred elderly patients have participated in clinical studies with ZOLOFT. The pattern of adverse reactions in the elderly was similar to that in younger patients. **ADVERSE REACTIONS** ***Commonly Observed:*** The most commonly observed adverse events associated with the use of ZOLOFT (sertraline hydrochloride) and not seen at an equivalent incidence among placebo-treated patients were: gastrointestinal complaints, including nausea, diarrhea/loose stools and dyspepsia; tremor; dizziness; insomnia; somnolence; increased sweating; dry mouth; and male sexual dysfunction (primarily ejaculatory delay). ***Associated with Discontinuation of Treatment:*** Fifteen percent of 2710 subjects who received ZOLOFT in premarketing multiple dose clinical trials discontinued treatment due to an adverse event. The more common events (reported by at least 1% of subjects) associated with discontinuation included agitation, insomnia, male sexual dysfunction (primarily ejaculatory delay), somnolence, dizziness, headache, tremor, anorexia, diarrhea/loose stools, nausea, and fatigue. ***Incidence in Controlled Clinical Trials:*** The table that follows enumerates adverse events that occurred at a frequency of 1% or more among ZOLOFT patients who participated in controlled trials comparing titrated ZOLOFT with placebo. Most patients received doses of 50 to 200 mg per day.

Treatment-Emergent Adverse Experience Incidence in Placebo-Controlled Clinical Trials*

Adverse Experience	ZOLOFT (N=861) (Percent of Patients Reporting)	Placebo (N=853) (Percent of Patients Reporting)
Autonomic Nervous System Disorders		
Mouth Dry	16.3	9.3
Sweating Increased	8.4	2.9
Cardiovascular		
Palpitations	3.5	1.6
Chest Pain	1.0	1.6
Central and Peripheral Nervous System Disorders		
Headache	20.3	19.0
Dizziness	11.7	6.7
Tremor	10.7	2.7
Paresthesia	2.0	1.8
Hypoesthesia	1.7	0.6
Twitching	1.4	0.1
Hypertonia	1.3	0.4
Disorders of Skin and Appendages		
Rash	2.1	1.5
Gastrointestinal Disorders		
Nausea	26.1	11.8
Diarrhea/Loose Stools	17.7	9.3
Constipation	8.4	6.3
Dyspepsia	6.0	2.8
Vomiting	3.8	1.8
Flatulence	3.3	2.5
Anorexia	2.8	1.6
Abdominal Pain	2.4	2.2
Appetite Increased	1.3	0.9
General		
Fatigue	10.6	8.1
Hot Flushes	2.2	0.5
Fever	1.6	0.6
Back Pain	1.5	0.9
Metabolic and Nutritional Disorders		
Thirst	1.4	0.9
Musculoskeletal System Disorders		
Myalgia	1.7	1.5
Psychiatric Disorders		
Insomnia	16.4	8.8
Sexual Dysfunction-Male (1)	15.5	2.2
Somnolence	13.4	5.9
Agitation	5.6	4.0
Nervousness	3.4	1.9
Anxiety	2.6	1.3
Yawning	1.9	0.2
Sexual Dysfunction-Female (2)	1.7	0.2
Concentration Impaired	1.3	0.5
Reproductive		
Menstrual Disorder (2)	1.0	0.5
Respiratory System Disorders		
Rhinitis	2.0	1.5
Pharyngitis	1.2	0.9
Special Senses		
Vision Abnormal	4.2	2.1
Tinnitus	1.4	1.1
Taste Perversion	1.2	0.7
Urinary System Disorders		
Micturition Frequency	2.0	1.2
Micturition Disorder	1.4	0.5

*Events reported by at least 1% of patients treated with ZOLOFT are included.
(1) - % based on male patients only: 271 ZOLOFT (primarily ejaculatory delay) and 271 placebo patients.
(2) - % based on female patients only: 590 ZOLOFT and 582 placebo patients.

Other Events Observed During the Premarketing Evaluation of ZOLOFT (sertraline hydrochloride): During its premarketing assessment, multiple doses of ZOLOFT were administered to approximately 2700 subjects. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Events of major clinical importance are also described in the PRECAUTIONS section. **Autonomic Nervous System Disorders**—*Infrequent:* flushing, mydriasis, increased saliva, cold clammy skin; *Rare:* pallor. **Cardiovascular**—*Infrequent:* postural dizziness, hypertension, hypotension, postural hypotension, edema, dependent edema, periorbital edema, peripheral edema, peripheral ischemia, syncope, tachycardia; *Rare:* precordial chest pain, substernal chest pain, aggravated hypertension, myocardial infarction, varicose veins. **Central and Peripheral Nervous System Disorders**—*Frequent:* confusion; *Infrequent:* ataxia, abnormal coordination, abnormal gait, hyperesthesia, hyperkinesia, hypokinesia, migraine, nystagmus, vertigo; *Rare:* facial anesthesia, coma, convulsions, dyskinesia, dysphonia, hyporeflexia, hypotonia, ptosis. **Disorders of Skin and Appendages**—*Infrequent:* acne, alopecia, pruritus, erythematous rash, maculopapular rash, dry skin; *Rare:* bullous eruption, dermatitis, erythema multiforme, abnormal hair texture, hypertrichosis, photosensitivity reaction, follicular rash, skin discoloration, abnormal skin odor, urticaria. **Endocrine Disorders**—*Rare:* exophthalmos, gynecomastia. **Gastrointestinal Disorders**—*Infrequent:* dysphagia, eructation; *Rare:* diverticulitis, fecal incontinence, gastritis, gastroenteritis, glossitis, gum hyperplasia, hemorrhoids, hiccup, melena, hemorrhagic peptic ulcer, proctitis, stomatitis, ulcerative stomatitis, tenesmus, tongue edema, tongue ulceration. **General**—*Frequent:* asthenia; *Infrequent:* malaise, generalized edema, rigors, weight decrease, weight increase; *Rare:* enlarged abdomen, halitosis, otitis media, aphthous stomatitis. **Hematopoietic and Lymphatic**—*Infrequent:* lymphadenopathy, purpura; *Rare:* anemia, anterior chamber eye hemorrhage. **Metabolic and Nutritional Disorders**—*Rare:* dehydration, hypercholesterolemia, hypoglycemia. **Musculoskeletal System Disorders**—*Infrequent:* arthralgia, arthrosis, dystonia, muscle cramps, muscle weakness; *Rare:* hernia. **Psychiatric Disorders**—*Infrequent:* abnormal dreams, aggressive reaction, amnesia, apathy, delusion, depersonalization, depression, aggravated depression, emotional lability, euphoria, hallucination, neurosis, paranoid reaction, suicide ideation and attempt, teeth-grinding, abnormal thinking; *Rare:* hysteria, somnambulism, withdrawal syndrome. **Reproductive**—*Infrequent:* dysmenorrhea (2), intermenstrual bleeding (2); *Rare:* amenorrhea (2), balanoposthitis (1), breast enlargement (2), female breast pain (2), leukorrhea (2), menorrhagia (2), atrophic vaginitis (2).

(1) - % based on male subjects only: 1005; (2) - % based on female subjects only: 1705.

Respiratory System Disorders—*Infrequent:* bronchospasm, coughing, dyspnea, epistaxis; *Rare:* bradypnea, hyperventilation, sinusitis, stridor. **Special Senses**—*Infrequent:* abnormal accommodation, conjunctivitis, diplopia, earache, eye pain, xerophthalmia; *Rare:* abnormal lacrimation, photophobia, visual field defect. **Urinary System Disorders**—*Infrequent:* dysuria, face edema, nocturia, polyuria, urinary incontinence; *Rare:* oliguria, renal pain, urinary retention. **Laboratory Tests** In man, asymptomatic elevations in serum transaminases (SGOT [or AST] and SGPT [or ALT]) have been reported infrequently (approximately 0.8%) in association with ZOLOFT administration. These hepatic enzyme elevations usually occurred within the first 1 to 9 weeks of drug treatment and promptly diminished upon drug discontinuation. ZOLOFT therapy was associated with small mean increases in total cholesterol (approximately 3%) and triglycerides (approximately 5%), and a small mean decrease in serum uric acid (approximately 7%) of no apparent clinical importance. **DRUG ABUSE AND DEPENDENCE** ***Controlled Substance Class*** - ZOLOFT (sertraline hydrochloride) is not a controlled substance. ***Physical and Psychological Dependence*** - ZOLOFT has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. However, the premarketing clinical experience with ZOLOFT did not reveal any tendency for a withdrawal syndrome or any drug-seeking behavior. As with any new CNS active drug, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of ZOLOFT misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior). **OVERDOSAGE** ***Human Experience*** - There have been 3 cases of ZOLOFT (sertraline hydrochloride) overdosage (approximately 750-2,100 mg). No specific therapy was required for any of the 3 patients, all of whom recovered completely. ***Management of Overdoses*** - Establish and maintain an airway, insure adequate oxygenation and ventilation. Activated charcoal, which may be used with sorbitol, may be as or more effective than emesis or lavage, and should be considered in treating overdose. Cardiac and vital signs monitoring is recommended along with general symptomatic and supportive measures. There are no specific antidotes for ZOLOFT. Due to the large volume of distribution of ZOLOFT, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center on the treatment of any overdose.

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1993

Western Scientific Assembly

ANNUAL SESSION

February 26 – March 3, 1993
Disneyland Hotel, Anaheim

The 1993 Annual Session and

GOLDEN APPLE AWARD AND RECEPTION

"THE CRISIS IN CLINICAL ACADEMIC MEDICINE"

Friday, February 26, 5:30 pm

DOCTOR THOMAS C. CESARIO has been selected by the Committee on Scientific Assemblies to receive CMA's 1993 Golden Apple Award. This award spotlights exceptional physicians who have made a lifelong commitment to teaching and are renowned for their charismatic, scientific and educational talents.

A native of Wisconsin, where he received his medical education, Doctor Cesario completed his postgraduate education and fellowship training in Boston, MA. He joined the faculty of the University of California, Irvine in 1971, becoming Professor of Medicine in 1984. He continues to serve as director of several clinical and academic programs, and has been appointed Interim Chairman of the Department of Medicine and Director of UCI's Residency Program in Internal Medicine.

Though virology has been the focus of his research and the subject of dozens of articles over the years, Doctor Cesario has always had an affinity and talent for teaching. In this regard, his impact on UCI medical students was virtually immediate. He received his first award for teaching in 1973 and has been so honored 10 times. Clinician-academician-teacher. This clearly epitomizes Doctor Cesario's distinguished medical career.

We encourage all to attend CMA's Golden Apple Award presentation and reception as Doctor Cesario explores this "Crisis in Clinical Academic Medicine".

The financial assistance of Cooperative of American Physicians, Inc. - Mutual Protection Trust is gratefully acknowledged in making this reception possible.

FRIDAY, FEBRUARY 26

01 Basic Cardiac Life Support

02 Update in Internal Medicine

03 Diagnosis of Common Office Gynecological Problems

04 HIV Prevention, Detection, and Early Management

05 How to Cope with the New Standards for Bloodborne Pathogens and CLIA

06 Current Screening Technologies and Controversies

07 The Brain and Spine in Sports Injuries: Neurosurgical Implications of Athletic Trauma

08 Difficult Wound Problems and Their Management

09 What You Always Should Have Known About Your Patients' Private Lives,

But Didn't Know How To Ask - Taking a Sexual and Drug History

SATURDAY, FEBRUARY 27

10 Advanced Cardiac Life Support: Provider Course

11 Bites, Burns, Bruises, and Bumps: Skin Problems of the Active Patient

12 Hippocrates or Hippocracy? Is Pain Control Adequate?

13 Ophthalmology: Key Issues for the Primary Care Physician

14 Medical Treatment of Common Neurological Symptoms

15 The Disruptive Physician: Dilemmas for the Medical Staff

16 Update on Surgery

17 Update on the Foot and Ankle

18 Advances in the Management of Common Pediatric Problems

Western Scientific Assembly

SUNDAY, FEBRUARY 28

19 Advanced Cardiac Life Support - Provider Retraining

20 Urology for Primary Care Physicians

21 What's New and Clinically Important in Allergy and Clinical Immunology

22 Current Topics in Hearing and Balance

23 Suture Course

24 Imaging Choices 1993

25 Algorithms for Alcoholics

26 Target Intervention: How To Help Your Patients Stop Smoking

27 Medical and Surgical Treatment of Rhinitis and Sinusitis

28 Carpal Tunnel Syndrome: Old Disease - New Prevalence and Controversies

29 All You Want to Know About the Match: A Workshop on Residency Selection and Career Planning

30 Professional Liability Issues in Breast Cancer and Implants

31 Bridging the Gap - Tobacco Intervention for Special Populations

MONDAY, MARCH 1

32 New Frontiers in Family Medicine: Selected Topics for Primary Care Physicians

33 High-Tech Rehabilitation: The Final Frontier

34 A Doctor's Dilemma - How to Deal with the "Difficult" Patient

35 Sleep - From A To ZZZ

36 Planning for Retirement and a Stable Financial Future

To receive a copy of the 40-page Advance Program Guide, which provides details on all programs below, please call (415) 882-3384.

CMA Council on Legislation and AMA Council on Legislation presents

A CRITICAL LOOK AT THE WASHINGTON SCENE

Sunday, February 28

Program Planners and Moderators: *Richard F. Corlin, MD*, President of the California Medical Association; Sidney E. Foster, MD, Chair, Council on Legislation

Educational Objectives: This program will provide CMA members with firsthand information on federal health policy direction. Both a representative from the Administration and a U.S. Senator or Representative with a key role in deciding health policy and/or budget issues will be invited to participate in a panel presentation focusing on upcoming federal health issues. The workings of the AMA Council on Legislation vis-a-vis the AMA Board of Trustees will also be discussed.

1:30 **Welcome and Introduction**

1:40 **AMA Overview of the Workings of the AMA Council on Legislation**

1:50 **Administration/Congressional Presentations**

3:15 **AMA Perspective and Reaction**

AMA Overview of Important Federal Issues

3:45 **Audience Questions and Answers**

4:30 **Adjournment**

EXHIBITS

During the Western Scientific Assembly, the Exhibit Hall will feature exhibits for everyone: pharmaceuticals, educational displays, computer systems, office systems, insurance, investment opportunities, medical testing systems, health and home products, and much more.

CONCURRENT EVENTS

CMA HOUSE OF DELEGATES

The CMA House of Delegates meets each day, Saturday, February 27 through Wednesday, March 3. House Speaker, Doctor Jack McCleary, notes that the current schedule of the House provides delegates with time to attend scientific programs, view the exhibits and participate in delegation caucuses.

Highlights of this year's House will be the farewell address of outgoing CMA President, Richard F. Corlin, MD, a Santa Monica gastroenterologist, and the inaugural address of CMA's President-Elect, David R. Holley, MD, a Monterey radiologist.

YOUNG PHYSICIANS SECTION ANNUAL ASSEMBLY

All California physicians under 40 years of age or in their first five years of practice are invited to attend the CMA Young Physicians Section (YPS) Annual Assembly. The Assembly debates resolutions on a myriad of medical practice and health policy issues and forwards is recommendations to the CMA House of Delegates, the AMA, or its own Executive Committee for action. The 1993 CMA-YPS Assembly will incorporate a Young Physicians Leadership Conference into the Section's own representative assembly and annual elections. Registration will begin at 7:30 am on Friday, February 26 at the Disneyland Hotel, and the Assembly will convene from 8:30 am to 5:30 pm. For additional information, please contact Roger Purdy at (416) 882- 5127.

CMA HOSPITAL MEDICAL STAFF SECTION ANNUAL ASSEMBLY

Medical staff leaders from throughout the state will come together at the 1993 CMA-HMSS Annual Assembly to discuss issues of vital concern to hospital medical staff physicians. In addition to updates on legal and legislative issues, this year's conference will feature presentations on changes in the medical practice environment, including the impact of hospital mergers, buy-outs, managed care, and contracting. For more information about the HMSS agenda and registration fees, call (415) 882-3384 for a copy of the Advance Program.

GENERAL INFORMATION

LOCATION

The CMA 1993 Western Scientific Assembly will be held at the Disneyland Hotel, 1150 West Cerritos Avenue, Anaheim, CA 92802. Call (714) 778-6600 for hotel registration information and directions.

GENERAL REGISTRATION FEES FOR CMA MEMBERS AND NON-MEMBERS

The Western Scientific Assembly has long enjoyed a reputation of high quality continuing education at no cost to member physicians. Though the escalating costs of producing CME events of this size have forced CMA to require general registration fees for all attendees beginning this year, we believe that the Assembly continues to provide high quality, convenient, and economical CME courses.

All physicians and health professionals attending Western Scientific Assembly courses must pay general registration fees , with the exception of member medical students. Physicians and guests who do not attend any courses are not required to pay a fee. For a copy of the Advanced Program and a Registration fee schedule, please call (415) 882-3384.

ADVANCE REGISTRATION CLOSES FEBRUARY 1, 1993

Attendees may register on site at the Disneyland Hotel's Center Lounge:

Thursday, February 25, 1:00 pm to 7:00 pm
Friday, February 26, 7:00 am to 5:00 pm
Saturday, February 27, 7:00 am to 5:00 pm
Sunday, February 28, 7:00 am to 5:00 pm
Monday, March 1, 7:30 am to 3:00 pm

On Tuesday, March 2, the registration desk will move to the House of Delegates Registration Area outside the Marina Ballroom from 9:00 am to 12:00 noon.

FOR MORE INFORMATION

Contact CMA, Western Scientific Assembly (415) 882-3384

ABSTRACTS JANUARY 1993

(Danoff NL, Kemper KJ: Does excluding patients without telephones affect the results of telephone reminder studies? West J Med 1993 Jan; 158:44-46)

Studies of the effectiveness of telephone reminders to improve the rate of appointments kept have shown conflicting results. Few have accounted for patients without telephones. We conducted a controlled clinical trial to study the effect of excluding patients without telephones in a study of telephone reminders in an urban pediatric clinic. Telephone reminders were attempted the evening before scheduled visits for 238 subjects; 259 controls received no reminders. The overall rate of kept appointments was the same (54%) for both the intervention group and the control group. In neither group was there a substantial difference in the "show" rate between patients with and without telephones (intervention group 52% versus 57%, control group 55% versus 54%). In the intervention group, the show rate was higher for those with telephones who were contacted (66%) than for those who were not (37%) ($P < .001$). Telephone reminders did not improve the overall rate of kept appointments but appeared to result in a significant improvement in the show rate of those who could be reached. Excluding patients who could not be reached by telephone may affect the usefulness of previous studies.

TELEPHONE REMINDERS PRACTICE MANAGEMENT

(Danoff NL, Kemper KJ: Does excluding patients without telephones affect the results of telephone reminder studies? West J Med 1993 Jan; 158:44-46)

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TELEPHONE REMINDERS PRACTICE MANAGEMENT

Three copies of this abstract are provided to help you in filing and cross-referencing research articles.

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CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

May 7-8—**Asthma and Allergy in the 1990s.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 10 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

ANESTHESIOLOGY

January 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Westin Maui, Kaanapali Beach, Maui, Hawaii. 1 wk. 21 hrs. $395. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

January 29-31—**31st Clinical Conference in Pediatric Anesthesiology.** Children's Hospitals Los Angeles at Disneyland Hotel, Anaheim. Fri-Sun. 15 hrs. Contact: David Steward, Children's Hospital, PO Box 54700, Los Angeles 90054. (213) 669-2262.

March 19-23—**67th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Diego Marriott Hotel & Marina, San Diego. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131-2553. (216) 642-1124.

March 26-28—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort, Dana Point. Fri-Sun. 9 hrs. $175-$245. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

May 23-28—**Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

January 21-23—**Cardiology '93.** Scripps Memorial Hospital Cardiovascular Institute at La Jolla Marriott. Thurs-Sat. Contact: Janice Turner, Conference Manager, PO Box 2586, La Jolla 92038. (619) 459-1564.

January 21-23—**Clinical Nuclear Cardiology: Case Review With the Experts.** American College of Cardiology at Cedars-Sinai Medical Center, Los Angeles. Thurs-Sat. 22 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

January 22-23—**Arrhythmias: Interpretation, Diagnosis and Management.** American College of Emergency Physicians at Las Vegas, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

February 5-6—**Cardiology 1993: Concepts and Controversies.** Mercy Heart Institute at Hyatt Regency, Sacramento. Fri-Sat. 7 hrs. $35. Contact: Mercy Heart Institute, (916) 733-6966.

February 19-20—**Arrhythmias: Interpretation, Diagnosis and Management.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 11-13—**3rd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 26-27—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 2-3—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Le Meridien Hotel, San Diego. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 23-24—**Coronary Heart Disease Update.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

May 7-8—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Parc 55 Hotel, San Francisco. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

CARDIOVASCULAR DISEASE

January 21-22—**Pulmonary-Esophageal Interactions: Acidity, Aspiration and Lung Disease.** California Thoracic Society at Doubletree Resort, Palm Springs. Thurs-Fri. 11 hrs. $320. Contact: CTS, 202 Fashion Ln, Ste 219, Tustin 92680. (714) 730-1944.

March 26-28—**Thromboembolic and Primary Pulmonary Vascular Disease: Diagnosis and Management.** UCSD at Sheraton Harbor Island Hotel, San Diego. Fri-Sun. 18 hrs. $500. Contact: Shirley Kolkey, 9606 Tierra Grande, #106, San Diego 92126. (619) 271-6673.

June 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marriott Hotel, Monterey. Fri-Sun. 12 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

KEY TO ABBREVIATIONS

CMA California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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June 25-26—**Advances in Vascular Diseases.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

January 15-17—**Practical Dermatology and Dermatologic Office Procedures for the Primary Care Physician.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. Contact: UCSD.

January 22-24—**Cutaneous Malignancies: 1993 Skin Cancer Update.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 18 hrs. $350. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

January 14-17—**The California Trauma Conference.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 20 hrs. $400. Contact: UCSD.

January 18-22—**Emergency Medicine Symposia I.** UCSD at San Diego Hilton. Mon-Fri. Contact: UCSD.

January 23-30—**Wound Management.** UCSD at Royal Waikoloan, Kohala Coast, Island of Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Royal Lahaina Resort, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 21-26—**Emergency Medicine: 1993.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $465. Contact: UCD.

March 7-12—**13th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 15-19—**Emergency Medicine Symposia II.** UCSD at La Jolla. Mon-Fri. Contact: UCSD.

March 24-28—**Winter Wilderness Medicine: 1993.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (800) 888-5632.

March 31-April 3—**Advances in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Wed-Sat. 19 hrs. Contact: UCSF.

May 10-14—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 12-16—**Wound Management Workshop for Primary Care Physicians.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $475. Contact: UCSD.

ENDOCRINOLOGY/METABOLISM

January 20—**Diabetes Symposium.** Enloe Hospital at The Esplanade Building, Chico. Wed. Contact: Linda Spring, (916) 891-7375.

February 19-20—**New Horizons in Diabetes Therapy.** Scripps Clinic and Research Foundation at Scripps Memorial Hospital, La Jolla. Fri-Sat. $175. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5—**19th Annual Diabetes Symposium.** UCD at Sheraton Sunrise, Rancho Cordova. Fri. 6 hrs. Contact: UCD.

March 10-11—**Advances in Endocrinology and Metabolism.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 11-13—**Treating the Disease of Obesity: Dilemmas and Decisions for the Health Care Professional.** UCLA at Miramar Sheraton Hotel, Santa Monica. Thurs-Sat. 17 hrs. $262. Contact: UCLA Extension.

March 12-13—**Diabetes Update.** UCSF at Ritz-Carlton Hotel, San Francisco. Fri-Sat. 11 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 12-14—**Office Gynecology for the Primary Care Physician.** San Diego State University at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

February 12-15—**45th Annual Scientific Assembly.** California Academy of Family Physicians at Wyndham Hotel and Palm Springs Convention Center. Fri-Mon. 25.5 hrs. Contact: Robert Fagan, CAFP, 114 Sansome St, Ste 1305, San Francisco 94104. (415) 394-9121.

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SPONSORED BY THE AMERICAN ENVIRONMENTAL HEALTH FOUNDATION

February 20—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium. Sat. 6 hrs. Contact: UCD.

March 24-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Fri. 15.5 hrs. $300. Contact: UCSF, Department of Family and Community Medicine.

April 10-17—**Primary Care Medicine: Update 1993.** UCSF at Maui Inter-Continental Hotel, Wailea, Hawaii. 1 week. 20 hrs. $545. Contact: UCSF.

April 22-24—**Rheumatology for Primary Care Physicians.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 14 hrs. Contact: UCSF.

April 22-25—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 23-25—**Family Practice: Today and Tomorrow.** UCSD at San Diego Hilton. Fri-Sun. 14 hrs. $150. Contact: UCSD.

GERIATRICS

January 19-22—**Intensive Course in Geriatric Medicine.** UCLA at Ritz-Carlton Hotel, Marina del Rey. Tues-Fri. 29 hrs. $625. Contact: UCLA.

February 4-5—**Alzheimer's Disease New Advances in Treatment.** UCSD at San Diego. Fri-Sat. Contact: UCSD.

HEMATOLOGY

February 14-17—**Clinical Hematology and Oncology: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sun-Wed. 18 hrs. $385. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 11-13—**Recent Advances in Autologous Hematopoietic Stem Cell Transplantation.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sat. 16 hrs. $300. Contact: UCSD.

March 17-20—**5th International Symposium on Blood Substitutes.** UCSD at Sheraton Harbor Island. Wed-Sat. Contact: UCSD.

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CONTINUING MEDICAL EDUCATION

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April 25-28—**10th Scientific Meeting of the Inter-American Society of Hypertension.** UCSD at Sheraton-Grande Torrey Pines. Sun-Wed. 39 hrs. $300. Contact: UCSD.

April 28—**World Hypertension League Symposium.** UCSD at Sheraton-Grande Torrey Pines. Wed. 4 hrs. Contact: UCSD.

INFECTIOUS DISEASES

January 12-23—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1½ weeks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

February 1-5—**Advanced—STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Fri. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

February 5-6—**11th Annual Practical Update of Infectious Diseases.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. 12 hrs. $160. Contact: UCD.

March 16-18—**Planning and Evaluation HIV Programs.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 23-25—**STD/HIV for Outreach Workers.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 30-31—**HIV Update.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Wed. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 12-24—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1¾ wks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 28-30—**Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. Contact: UCSF.

May 24-29—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Sat. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

INTERNAL MEDICINE

January 28-30—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at La Jolla Marriott. Sat-Mon. Contact: UCSD.

February 5-7—**State of the Art Urology.** UCLA at Ritz-Carlton, Marina del Rey. Fri-Sun. Contact: UCLA Extension.

February 6—**California Association of Cytology.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

February 20-25—**Topics and Advances in Internal Medicine.** UCSD at Hyatt Regency, San Diego. Sun-Thurs. 45 hrs. $595. Contact: UCSD.

February 26-27—**Advances in Vascular Diseases.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 1-5—**31st Annual Critical Care Medicine.** USC at Caesar's Palace, Las Vegas, Nevada. Mon-Fri. 25 hrs. $595-$680. Contact: USC.

March 19-25—**Internal Medicine 1993: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Tues. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5-8—**Controversies and Agreements in Internal Medicine.** Group Health Cooperative at Intercontinental Hotel, Maui, Hawaii. Mon-Thurs. 19 hrs. $425. Contact: GHC, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

NEUROLOGY

February 4-6—**16th Annual: Neurology for Non-Neurologists.** UCSD at Doubletree Hotel Horton Plaza, San Deigo. Thurs-Sat. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 11-13—**26th Annual Recent Advances in Neurology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 15 hrs. $345. Contact: UCSF.

February 27—**Evaluation and Management of the Dizzy Patient.** UCLA at Neuropsychiatric Institute Auditorium. Sat. 5.5 hrs. $65. Contact: UCLA Extension.

March 19-21—**Advances in Clinical Neuroscience Symposium.** Hospital of the Good Samaritan at Rancho Las Palmas Resort, Rancho Mirage. Fri-Sun. Contact: Hospital of the Good Samaritan, 616 S Witmer St, Los Angeles 90017-2395. (213) 977-2335.

May 14-16—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sun. 12 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

June 12-14—**Pharmacological Approaches to the Treatment of Chronic Pain: Current Concepts and Critical Issues.** UCSF at Doubletree Fisherman's Wharf, Monterey. Sat-Mon. Contact: UCSF.

OB/GYN

January 17-19—**Annual Ambulatory Gynecology Update: 1993.** UCD at Incline Village, Nevada. Sun-Tues. 14 hrs. $260. Contact: UCD.

February 11-14—**48th Annual Postgraduate Assembly.** Obstetrical and Gynecological Assembly of Southern California at Beverly Hilton, Beverly Hills. Thurs-Sun. 28 hrs. Contact: C. James Dowden, OB/GYN Assembly, 5820 Wilshire Blvd, #500, Los Angeles 90036. (213) 937-5514.

February 17-19—**Contemporary Obstetrical and Transvaginal Ultrasound.** UCSD. Wed-Fri. Contact: UCSD.

March 18-20—**Prevention of Prematurity and Neonatal Mortality.** UCSD at Loew's Coronado. Thurs-Sat. 13 hrs. $370. Contact: UCSD.

April 14-18—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Susan Butler, PCFS, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

January 25-February 5—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. 1½ weeks. 80 hrs. $1400. Contact: UCSF.

February 8-12—**Occupational and Environmental Medicine: Session III.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

March 4-5—**Dimensions of Caring 1993: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Doubletree Hotel Horton Plaza, La Jolla. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-9592.

OPHTHALMOLOGY

January 30—**Genetic Disease and the Eye.** Cedars Sinai Medical Center Division of Ophthalmology at Ma Maison Hotel, Los Angeles. Sat. 8 hrs. $50. Contact: Yaron Rabinowitz, MD, 444 S San Vicente Blvd, Ste 600, Los Angeles 90048. (310) 855-2613.

February 26-27—**7th Annual Visions in Ophthalmology Symposium.** Mericos Eye Institute at Scripps Memorial Hospitals. Fri-Sat. 12 hrs. Contact: Sheila Seid, 3030 Children's Way, Ste 402, San Diego 92123. (619) 974-6780.

May 14-15—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OTOLARYNGOLOGY

January-April 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Sun-Fri. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

February 19-21—**Midwinter Clinical Conference for Otolaryngologists and Ophthalmologists.** Research Study Club of Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Fri-Sun. 15 hrs. Contact: Research Study Club, PO Box 1216, Murrieta 92564. (714) 677-4482.

June 23-25—**20th International Conference on Cochlear Implants.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. Contact: UCSF.

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PATHOLOGY

January 25-29—**American Society of Clinical Pathologists Workshop Week in Medical Technology.** ASCP at Airport Hilton, San Francisco. Mon-Fri. 7 hrs. Contact: ASCP, (800) 621-4142.

March 13—**Update on Dialysis Access: Creation, Maintenance and Salvage.** UCSD at Le Meridien. Sat. Contact: UCSD.

March 19-20—**Pathology Forum: 1993.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 17—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-6310.

May 27-29—**9th Annual Current Issues in Anatomic Pathology: 1993.** UCSF at Mark Hopkins Intercontinental Hotel Nob Hill, San Francisco. Thurs-Sat. 19.5 hrs. $450. Contact: UCSF.

PEDIATRICS

January 26-30—**San Diego Conference on Responding to Child Maltreatment.** Children's Hospital San Diego at Hyatt Regency, La Jolla. Tues-Sat. 28 hrs. Contact: Center for Child Protection, Children's Hospital, 8001 Frost St, San Diego 92123. (619) 495-4950.

February 15-17—**Pediatrics Update.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

February 26-28—**Current Concepts in Pediatric Medicine: 1993.** Children's Hospital San Diego and American Academy of Pediatrics at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Continuing Education, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 27-28—**Stabilization and Management of the Critically Ill Child.** UCSF at Grand Hyatt on Union Square, San Francisco. Sat-Sun. Contact: UCSF.

March 22-26—**Advanced Clinical Education in Child and Adolescent Obesity.** UCSF at San Francisco. Mon-Fri. 42 hrs. $350. Contact: UCSF.

April 2-3—**Ambulatory Pediatrics: Special Spotlight Morning in Neonatology.** UCD at Sacramento Inn. Fri-Sat. 10 hrs. Contact: UCD.

April 3-10—**Pediatrics Emergencies.** UCSD at Poipu Beach Hotel and Waiohai Resort, Kauai, Hawaii. 1 wk. 21 hrs. $450. Contact: UCSD.

May 13-15—**26th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 11-13—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 14 hrs. Contact: Children's Hospital, (619) 576-4072.

PSYCHIATRY

January 24-29—**19th Annual Midwinter Program for Psychiatrists: Special Focus on Hysteria.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $395. Contact: UCD.

February 12-14—**West Coast Psychiatry Board Review: Preparation for Part II.** UCSD at Catamaran Hotel, San Diego. Fri-Sun. Contact: UCSD.

February 27—**Sleep Apnea: New Insights into Pathophysiology and Treatment.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 4-6—**51st Annual Meeting of the American Psychosomatic Society.** UCSD at Omni Hotel, San Diego. Thurs-Sat. Contact: UCSD.

April 24-25—**The Cutting Edge Conference 1993: The Treatment of Severe Personality Disorders.** UCSD at Doubletree Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

May 14-19—**The Power of Art: Introduction to Medical Hypnosis.** UCSD at Colonial Inn, Del Mar. Fri-Mon. 26 hrs. $595. Contact: UCSD.

RADIOLOGY

January 15-17—**45th Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Fri-Sun. 16.75 hrs. $125-$450. Contact: LARS, MWRC, PO Box 91215, Los Angeles 90009-1215. (310) 827-9078.

January 16-17—**Interventional Radiology Update.** Stanford University at Ritz-Carlton Hotel, Laguna Niguel. Sat-Sun. 7.5 hrs. $200-$250. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 18-20—**Neuroradiology Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Mon-Wed. 17.5 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

January 21-24—**Breast Imaging Update.** Stanford University at Ritz-Carlton Resort Hotel, Laguna Niguel. Thurs-Sun. 17.25 hrs. $400-$450. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 15-19—**Diagnostic Imaging Update: Mammography, MRI, Body Imaging, Neuroradiology, Pediatrics.** Stanford University Medical Center at Ritz-Carlton, Palm Beach. Mon-Fri. 23.75 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 22-26—**Diagnostic Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Kapalua Bay, Maui, Hawaii. Mon-Fri. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-27—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Wed-Sat. 15 hrs. $500. Contact: UCSD.

March 8-12—**8th Annual San Diego Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 29 hrs. $595. Contact: Dawne Ryals, PO Box 1925, Roswell 30077-1925. (404) 641-9773.

March 10-12—**13th Annual Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: Crest Organization (415) 595-2704.

March 13—**Focus on Hemodialysis Access: Creation, Maintenance and Salvage.** American College of Emergency Physicians at Le Meridien, San Diego (Coronado). Sat. 6.5 hrs. $75. Contact: UCSD.

March 15-17—**Squaw Valley Minimally Invasive Conference for Diagnostic Radiologists and Surgeons.** UCD at Resort at Squaw Creek, Squaw Valley. Mon-Wed. Contact: UCD.

March 28-April 2—**General Radiology Review Course.** UCLA at Doubletree Hotel, Marina del Rey. Sun-Fri. 40 hrs. $425. Contact: UCLA Department of Radiological Sciences.

April 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sat. 20 hrs. $500. Contact: UCSD.

April 18-23—**13th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 24—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8.25 hrs. $135. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

June 14-18—**MRI: A State-of-the-Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, San Francisco. Mon-Fri. 27 hrs. $650. Contact: STAN.

SURGERY

January 24-29—**16th Annual Postgraduate Assembly in Surgery.** UCSD at Doubletree Hotel, Horton Plaza, San Diego. Sun-Fri. Contact: UCSD.

February 18-23—**60th Annual Meeting of the American Academy of Orthopaedic Surgeons.** American Academy of Orthopaedic Surgeons at Moscone Center, San Francisco. Thurs-Tues. Contact: Alvin Nagelberg, (708) 384-4138.

March 17-20—**Surgical Challenges of the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at CMG Building, La Jolla. Wed-Sat. Contact: UCSD.

March 25-26—**General Thoracic Surgery.** American College of Chest Physicians at Caesar's Palace Hotel, Las Vegas, Nevada. Thurs-Fri. 13 hrs. $325-$375. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (708) 498-1400.

March 25-27—**Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

April 15-17—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

May 20-21—**8th Annual Neurosurgery Postgraduate Course: Intracranial Tumors—Modern Management.** UCSF at Grand Hyatt on Union Square. Tues-Thurs. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

January 22-23—**Nutritional Medicine in Medical Practice: Putting Nutrition to Work in the Prevention and Treatment of Common Diseases and Chronic Conditions.** UCLA at Miramar Sheraton Hotel, Santa Monica. Fri-Sat. 14 hrs. $165. Contact: UCLA Extension.

(Continued on Page 22)

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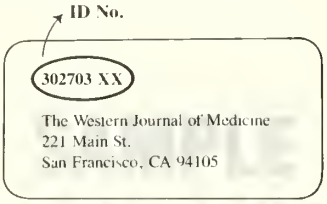

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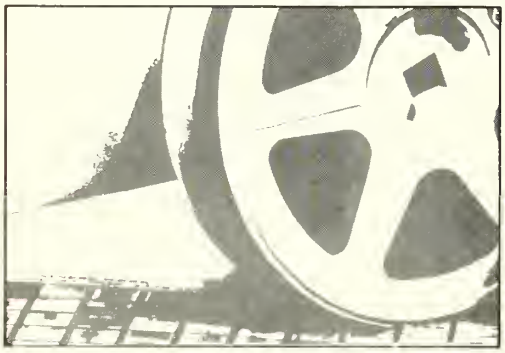

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(Continued from Page 21)

February 5-10—**61st Annual Postgraduate Convention.** Loma Linda Alumni Association at Campus. Fri-Wed. 32.5 hrs. Contact: Alumni Association, LLU, 11245 Anderson St, Loma Linda 92354. (714) 824-4633.

February 19-20—**Overcoming Barriers to Health Care Interventions.** UCLA at Sunset Village Conference Center, Westwood. Fri-Sat. 15.5 hrs. $75-$150. Contact: UCLA Extension.

February 22-26—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

March 19-20—**Annual Clinical Nutrition.** UCD at Berkeley Marina Marriott. Fri-Sat. Contact: UCD.

March 26-April 4—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. 1½ wks. Contact: UCLA Extension.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology and Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

January 22-24—**Contemporary Management of Unstable Coronary Syndromes.** Department of Veterans Affairs Medical Center at Beaver Run Resort and Conference Center, Breckenridge. Fri-Sun. Contact: Victoria Hall or Karen Babcock, (303) 393-2826, or FAX (303) 393-4656.

January 23-30—**Reconstructive Surgery of the Hip and Knee.** University of Colorado School of Medicine at Tamarron Resort, Durango. Sat-Sat. Contact: U of Colo.

January 29-30—**Fetal Assessment Conference.** Children's Hospital at University Hospital, Denver. Fri-Sat. Contact: Trish Beachy, (303) 270-8376.

February 13-20—**Primary Care Medicine: Concepts and Controversies.** University of California, San Francisco, School of Medicine, at Snowmass Conference Center, Snowmass. Sat-Sat. Contact: Virginia Turner, (415) 476-4251.

February 22-26—**Colorado Conference on Contemporary Family Practice.** University of Colorado School of Medicine at Breckenridge. Mon-Fri. Contact: U of Colo.

February 23—**Perinatal Update.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

February 26-March 1—**Principles of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Fri-Mon. Contact: U of Colo.

February 27-March 5—**Crash '93: Colorado Review of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Sat-Fri. Contact: U of Colo.

February 27-March 6—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Sat. Contact U of Colo.

CONTACT INFORMATION

U of Colo—Contact University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761

(Continued on Page 91)

epitome

i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a** : a summary of a written work **b** : a brief presentation or statement of something **2** : a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition — Richard Joseph) **3** : Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine*, now available in a single, bound volume.

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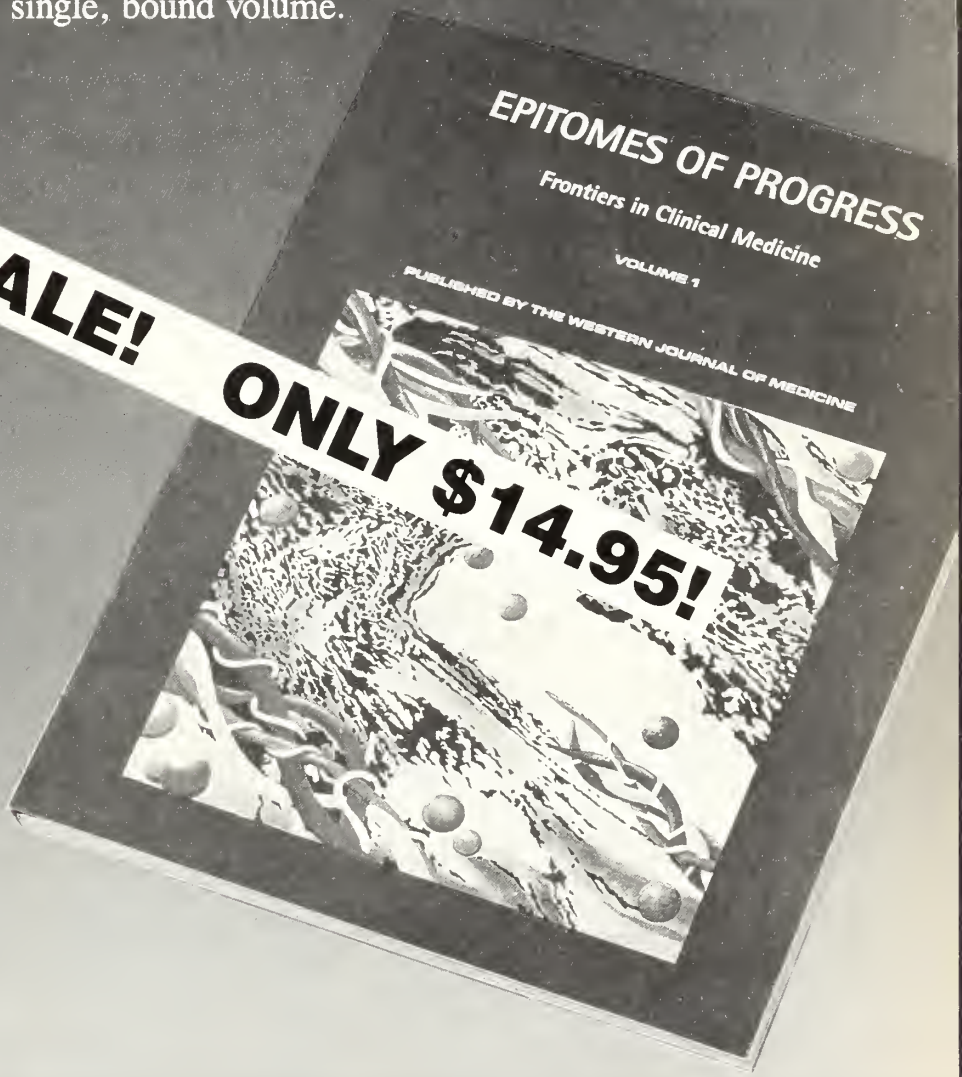

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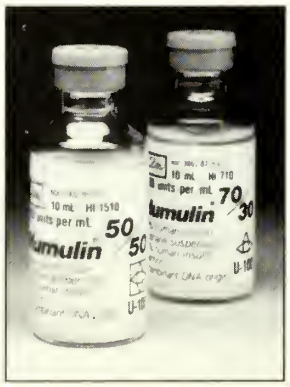

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Articles

Botulinum Toxin
From Poison to Medicine

LARRY E. DAVIS, MD, *Albuquerque, New Mexico*

Although thousands of people in the world each year continue to be poisoned with botulinum toxin—food-borne, infantile, or wound botulism—the neurotoxin is now sufficiently understood to allow it to be used as a medicinal agent to paralyze specific muscles, giving temporary symptomatic relief from a variety of dystonic neurologic disorders. I review some of the epidemiologic, clinical, and pathophysiologic aspects of botulinum toxin and how the neurotoxin may act as a poison or a medicine.

(Davis LE: Botulinum toxin—From poison to medicine. West J Med 1993 Jan; 158:25-29)

In the past several years, we have seen the following patients: A 43-year-old man who became flaccidly paralyzed two days after eating his wife's home-canned chilies; a previously healthy 4-month-old baby girl in whom diffuse weakness and constipation developed; a 50-year-old drug addict who subcutaneously inoculated heroin and in whom moderately severe weakness of all limbs and dysphasia developed; and a 45-year-old woman with severe blepharospasm who had pronounced relief of involuntary eyelid closures after her physician injected botulinum toxin (Botox) into the orbicularis oculi muscles. All four persons had exposure to the botulinum toxin. The first patient had food-borne botulism, the baby had infantile botulism, the heroin addict had "wound" botulism, and the last patient was therapeutically administered botulinum A toxin. In this article I review how the botulinum toxin can cause these clinical events.

Clostridium Botulinum

Clostridium botulinum are gram-positive, rod-shaped, spore-forming, strictly anaerobic bacteria that are widely distributed in soil and water.[1] Strains of *C botulinum* produce seven different neurotoxins and one binary toxin. Toxin types A, B, E, and F are the main toxins that affect humans.[1] Toxin types C and D cause botulism in birds and mammals.[2] *Clostridium botulinum* strains that produce toxin types A, B, and F are found generally in soil of geographic areas having low rainfall and moderate temperatures. Type A-producing bacteria are found primarily west of the Mississippi River and type B east of the Mississippi River.[2] Type E-producing bacteria are found in the marine life and sediment around fresh water, especially in Alaska and the Great Lakes region.[2]

Clostridium botulinum is a spore-forming bacterium. The spores are capable of surviving 100°C for at least six hours, but they are killed at temperatures of 120°C lasting five minutes.[3] The killing temperature of spores is important to the canning industry and was responsible for the practice of canning home foods in a pressure cooker. Home canning done after simply boiling the food is not sufficient to kill the spores. Under anaerobic or semianaerobic conditions, the spores can germinate, with progeny bacteria producing the botulinum toxin.[2]

The DNA necessary for *C botulinum* to produce the toxin may be in the host genome or come from either a bacteriophage or a plasmid. Removal of the phage or plasmid from *C botulinum* can result in a nontoxigenic bacterium.[4] Why *C botulinum* normally produces the botulinal toxin is unknown as infection of vertebrates is not part of the normal clostridial life cycle, and it has no known role in the growth or physiology of the organism.[5]

Botulinum Toxin

Botulinum toxin is a family of serologically closely related neurotoxins—A, B, C_1, D, E, F, and G. The primary structure of most serotypes has been determined. The toxins are mainly produced by different strains of clostridia,[2] but six other groups of physiologically distinct clostridia, such as *Clostridium barati* and *Clostridium butyricum*, have produced botulinum type E and F toxins.[6] On a milligram-per-kilogram basis, they are probably the most potent biologic toxins that affect humans. It has been estimated that 0.025 ng or 2×10^7 molecules of the botulinal toxin are sufficient to kill a mouse.[7] For comparison, it is estimated that 5×10^{13} molecules of α-bungarotoxin (cobra venom) and 2×10^{18} molecules of cyanide are required to kill a mouse.[8] For humans, about 0.3 ng or 10^{11} molecules of botulinum toxin reaching neuromuscular junctions are enough to cause clinical botulism.[9]

Botulinum toxin is odorless and tasteless. Unlike *C botulinum* spores, the toxin is heat-labile and is denatured by heating above 80°C.[3,10] It can resist destruction by stomach acid and digestion by enzymes in the gastrointestinal tract.

Botulinum toxin shares many properties with the other bacterial toxins such as tetanospasmin and diphtheria toxin.[11] Type A toxin is produced as a single-chain polypeptide with a molecular weight of 150,000.[11] Later it is transformed into its active structure by nicking with a protease to produce a dichain polypeptide of about 100,000 and 50,000 molecular weight.[12] There are three major domains in the molecule

From the Neurology Service, Veterans Affairs Medical Center, and Departments of Neurology and Microbiology, University of New Mexico School of Medicine, Albuquerque.
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Reprint requests to Larry E. Davis, MD, Veterans Affairs Medical Center, 2100 Ridgecrest Dr SE, Albuquerque, NM 87108.

ABBREVIATIONS USED IN TEXT

ADP = adenosine diphosphate
CDC = Centers for Disease Control

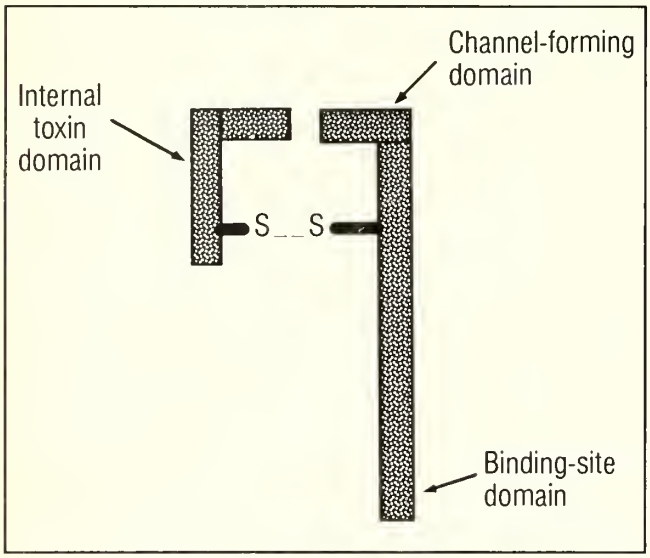

Figure 1.—The botulinum toxin molecule is composed of a heavy and a light chain with a total molecular weight of 150,000.

(Figure 1): The receptor binding site is at the carboxyterminus of the heavy chain (B_3). The channel-forming domain is the aminoterminus of the heavy chain. The internal toxin domain resides in the lighter chain, and the two chains are held together with a disulfide bond.

The pathophysiology of this toxin involves several steps: systemic absorption, binding to the nerve terminal, internalization, and synaptic poisoning. The toxin reaches the lymphatic channels first and then the bloodstream either by absorption through the upper gastrointestinal tract (food-borne and infantile botulism) or through tissue absorption (wound botulism).[9] The toxin then circulates in the blood until it reaches cholinergic synapses in the peripheral nervous system. The toxin appears not to cross the blood-brain barrier so central nervous system cholinergic synapses are not involved.[13] The toxin binds to the presynaptic side of the cholinergic synapse.[11,13] This binding step involves attachment of the carboxyterminus of the heavy chain of the toxin molecule to receptors on the presynaptic side of the synapse.[14] It has been estimated that there are about 150 to 600 binding sites per micrometer of presynaptic membrane.[8] Binding of the botulinal toxin to its receptor is of high affinity. Type-specific botulinum antibody is capable of neutralizing the toxin during the period (about ½ hour) between binding and internalization.[15] Internalization of the toxin occurs through receptor-mediated endocytosis.[8] In a final step, the botulinal toxin light chain crosses the membrane of the endocytic vesicle and enters the cytoplasm of the presynaptic terminal. As the pH in the vesicle falls below 4.0, a conformational change in the toxin molecule occurs. The heavy chain enters the vesical membrane to form a channel through which the light chain then passes into the cytoplasm (Figure 2).

On entrance of the light chain into the cytoplasm, the toxin induces dysfunction of the presynaptic terminal. Botulinum toxin blocks stimulus-induced and spontaneous quantal acetylcholine release by the presynaptic cholinergic synapse.[11,16] There is evidence that the inhibitory effect of the toxin occurs selectively at vesical release sites on the membrane of the presynaptic terminal. The blockage of the acetylcholine release results in muscle weakness.

The biochemical basis for the blockade of acetylcholine release is still unknown, but related bacterial toxins provide some clues. For many bacterial toxins, the toxic molecule appears to be an enzyme or regulatory protein. For example, anthrax toxin appears to be an adenylate cyclase.[17] The cholera toxin is an adenosine diphosphate (ADP)-ribosylating regulatory protein that stimulates adenylate cyclase.[18] The pertussis toxin is an ADP-ribosylating regulatory protein that inhibits adenylate cyclase.[18] The botulinum C_2 toxin (not a neurotoxin) appears to be an ADP-ribosyltransferase enzyme.[19] Thus the botulinal neurotoxins are likely to be enzymes that amplify inhibitory molecules or regulatory proteins that act to reduce quantal acetylcholine release.[5]

The blockade of quantal acetylcholine release by botulinal toxin may last several months. Synaptic acetylcholine transmission may recover through a turnover of critical presynaptic molecules by the cell or by the production of a new synapse through the sprouting of motoneuron axon terminals with the development of an adjacent new synapse on the same muscle fiber.[20,21]

Food-borne Botulism

Food-borne botulism accounts for most of the cases of botulinal intoxication. Food-borne botulism occurs when a person eats preformed toxin. Home foods, especially fruits and vegetables that are improperly processed, account for 90% of the cases of botulism.

Most outbreaks of type E botulism involve fish or fish products.[22] In Alaska, botulism among Native Americans has occurred from eating uncooked, dried, or fermented fish.[23]

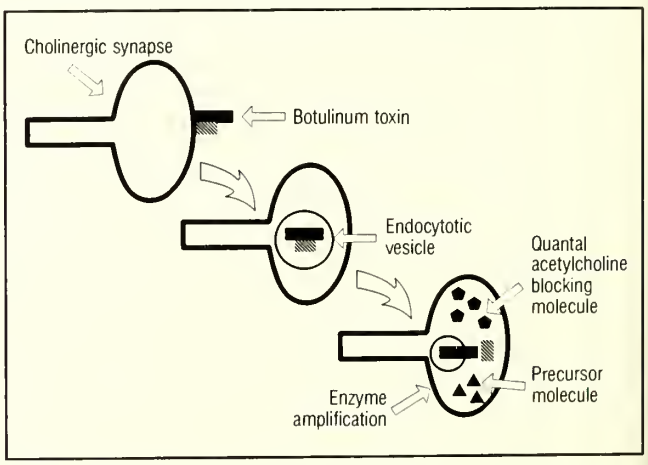

Figure 2.—Botulism poisoning involves 3 stages: binding of toxin to tissues, internalization of toxin, and internal synaptic poisoning. The internal poisoning step appears to involve the light chain acting as an enzyme to convert host proteins into inhibitory molecules or regulatory proteins that act to inhibit quantal acetylcholine release (from Simpson[5]).

After toxin ingestion, the mean incubation period is 2 days with a range of ½ to 6 days.[24] In general, the longer the incubation period, the milder the signs and symptoms. The classic clinical features of botulism include a descending symmetric paralysis of all skeletal muscles and many smooth

muscles.[2,24] Limb muscles become weak or completely paralyzed. Cranial nerve musculature is usually involved, resulting in an external ophthalmoplegia, dysarthria, dysphasia, ptosis, and facial weakness. In addition, patients have a dry mouth and often fixed dilated pupils. Weakness of respiratory muscles may be severe enough to require intubation and mechanical ventilation. Smooth muscle paralysis typically involves the gastrointestinal tract and bladder, resulting in constipation and at times paralytic ileus and urinary retention. Occasionally paresthesias or asymmetric limb weakness may develop.[25] The signs and symptoms of botulism usually progress over one to three days. There are several important negative clinical features of botulism. Because the toxin inactivates cholinergic synapses of the peripheral nervous system, patients usually have normal sensation, normal mentation, normal memory, and normal temperature, blood pressure, and heart rate.[2]

The botulinum toxin has been shown in experiments to bind to cholinergic synapses in brain homogenates and to block cholinergic transmission.[5] Patients do not show signs of central nervous system cholinergic blockade, however.[26] The difference may reflect the inability of the toxin to cross the blood-brain barrier or to block completely central nervous system cholinergic transmission.

Electrophysiologic studies are often helpful in the diagnosis of botulism. A modest increment in M-wave amplitude with rapid repetitive stimulation often occurs and may provide an early clue to the cause of the weakness.[27,28] Less specific changes include low-amplitude and short-duration motor unit action potentials with small M-wave amplitudes on an electromyogram. Single-fiber electromyography may show increased jitter and blocking.[27] Motor conduction velocities and distal latencies are normal. Patients with botulism usually have a normal hemogram, urinalysis, and cerebrospinal fluid.

The differential diagnosis of food-borne botulism includes the Guillain-Barré syndrome, diphtheric polyneuropathy, tick paralysis, curare poisoning, poliomyelitis, myasthenia gravis, and the Eaton-Lambert syndrome. If there is a cluster of patients with similar symptoms, botulism should be high in the differential diagnosis.

The laboratory diagnosis of botulism is made by analyzing specimens of serum (20 to 30 ml), stool (25 grams), and suspected food for the botulinum toxin.[2] Despite modern serologic tests such as the radioimmunoassay, the standard and most sensitive diagnostic test for the botulinum toxin is a biologic test involving mice. The number of toxin molecules needed to paralyze mouse neuromuscular junctions and to kill mice from respiratory failure is lower than the minimum amount of toxin that currently is needed for detection by standard serologic tests using antibodies against the botulinum toxin. The mouse test involves intraperitoneal inoculation of a mouse with the patient's serum or extracts of stool or food specimens to determine whether the mouse becomes paralyzed and dies.[2] Heating the specimen to 100°C or combining it with specific botulinum antitoxin should prevent the animal's death.

Treatment should begin as soon as the diagnosis of botulism is made. In many situations, a firm clinical diagnosis of botulism can be made even before the laboratory confirms the diagnosis. The treatment of food-borne botulism involves three steps: neutralize the circulating toxin; support the patient; and remove excess toxin, if possible, from the gastrointestinal tract. Because most cases of human botulism belong to types A, B, and E, it is possible to give equine anti-A, B, E serum to patients.[2] One vial (10 ml) should be given intramuscularly and the second vial intravenously. The antitoxin is not available in hospitals or at most state laboratories. In general, the antitoxin must be obtained from regional branches of the Centers for Disease Control (CDC). If botulism is suspected, the physician should contact the botulism officer at the CDC ([404] 639-3753, days; or [404] 639-2888, evenings and weekends). At that time, the public health officer can release the antitoxin from the nearest CDC branch to be placed on the next available commercial airline.

Equine botulinal antitoxin is extremely potent and is capable of neutralizing 10 to 1,000 times the amount of toxin that would be expected in the blood of most patients.[29] Because the antitoxin is of equine origin, the patient's skin should be tested with antitoxin first. There is about a 4% incidence of subsequent serum sickness.[30]

Botulinal antitoxin will not reverse existing clinical weakness as the toxin has already been internalized and is not accessible to antibody neutralization. Nevertheless, there does appear to be value in neutralizing any toxin that is still in the circulation. In one study, patients receiving the antitoxin on day 1 of their symptoms had fewer days on a respirator and shorter hospital stays than those receiving antitoxin after the first day.[31] To date, patients with botulism have not had a notable improvement from the administration of drugs that increase the release of acetylcholine from normal cholinergic synapses (guanidine, or 3,4-diaminopyridine) or that inhibit the breakdown of acetylcholine in the synaptic cleft (pyridostigmine).[32,33]

Because weakness may progress for several days, it is important to place patients in intensive care and monitor them carefully. Should respirations begin to fail, intubation and assisted ventilation are required. The respiratory weakness is often prolonged, necessitating a tracheostomy. Patients may have an ileus for several days, so feeding through a nasogastric tube should not begin until bowel sounds have returned. Frequently the bladder paralysis necessitates the use of an indwelling urinary catheter. It would be ideal to remove unabsorbed toxin from the gastrointestinal tract by the use of laxatives or enemas, but if gastrointestinal tract paralysis has occurred, this should not be undertaken.

Recovery from botulism is slow. Patients may be in the hospital for as long as six months and may be on a respirator for weeks to a few months. Even after hospital discharge, patients often complain of fatigue or dyspnea on exertion for at least a year. Muscle strength tests and pulmonary function tests are usually normal, however.[34] Patients who recover from botulism do not have antibodies to botulinum toxin, since the intoxication results from insufficient antigen to stimulate the immune system. The mortality from food-borne botulism has decreased in the United States primarily because of better intensive care. From 1900 to 1950 about 60% of patients died, whereas from 1970 to 1975 only 21% of persons died of food-borne botulism.[35]

Infantile Botulism

Infantile botulism results from the ingestion of clostridial spores that then colonize the gut to produce their neurotoxin directly in the gut.[36] The normal gastrointestinal tract of children and adults is remarkably resistant to colonization by clostridial bacteria. The gastrointestinal tract of infants 1

week to 11 months of age may, however, occasionally allow colonization of this organism. Factors influencing the vulnerability of the infant gut to colonization are poorly understood, but some infections occur when breast-feeding is changed to bottle-feeding. Under rare circumstances, adults have suffered a similar colonization of the gastrointestinal tract by clostridial organisms. In general, these adults have had their gut flora and pH altered by a surgical procedure or drugs.[37]

The average age of patients with infantile botulism is 3 months, but cases occur in infants 1 to 11 months.[38,39] Infants may have mild or severe disease.[40] Constipation from a partially paralyzed ileus usually develops first and can persist as long as three weeks before other symptoms appear.[38,41] A flaccid paralysis then develops, and the infants have a weak cry, poor suck, and a decreased interest in their environment. Loss of head control is a common early sign. Cranial nerve palsies are common, often producing ptosis, dilated pupils, facial diplegia, and impaired gag reflex.[38] Decreased respirations may develop, and respiratory assistance may be required. Deep tendon reflexes are decreased or absent. Autonomic involvement usually includes dry mucous membranes, decreased bowel motility, and urinary retention. The children are usually afebrile.

The differential diagnosis includes dehydration or electrolyte imbalance, diphtheric polyneuropathy, neonatal myasthenia gravis, poliomyelitis, hypothyroidism, tick paralysis, Werdning-Hoffmann spinal muscular atrophy, Leigh disease (subacute necrotizing encephalomyelopathy), congenital myopathy, the Guillain-Barré syndrome, and exposure to toxins such as heavy metals and organophosphates.[42]

Similar to those with food-borne botulism, patients with infantile botulism usually have reduced amplitude of their evoked compound muscle action potentials and incremental responses following repetitive nerve stimulation.[43]

The diagnosis of infantile botulism depends on the recovery of clostridial organisms and toxin from the stool.[2,44] Toxin and organisms may persist in the stool for a long time, even after clinical recovery.[45] Toxin is seldom detected in serum.[45]

The treatment of infantile botulism differs from food-borne botulism. Botulinal antitoxin has not affected the outcome of infantile botulism and is generally not given.[46] Similarly, penicillin or other antibiotic therapy has not affected the outcome of the disease.[38,47] Aminoglycoside antibiotics are contraindicated because they increase presynaptic muscular blockade and may worsen the paralysis.[48] Therefore, treatment is excellent supportive care in an intensive care unit. Because the infant stool contains viable clostridia, care should be taken not to cross-infect other infants in the intensive care unit. Infants usually recover spontaneously over several weeks. Currently less than 3% of patients in hospital die.[46]

The age distribution of the sudden infant death syndrome parallels that of infantile botulism.[40] Studies of infants dying of the sudden infant death syndrome have shown that about 5% have evidence of intestinal infection with *C botulinum*, suggesting that infantile botulism may be one cause of the syndrome.[40,41] It should be noted that *C botulinum* organisms have also been identified in healthy infants without signs of botulism.[38]

Wound Botulism

Wound botulism is the least common type of botulinal intoxication. Wound botulism occurs when *C botulinum* replicates in an abscess that has an anaerobic environment producing botulinal toxin that becomes systemically absorbed. Wound botulism is a rare disease in the United States and occurs most often from subcutaneous abscesses or deeper wound infections in muscle, nerves, and soft tissues.[49] At present, most cases occur in drug abusers who subcutaneously inject street drugs ("skin popping")[50] or following penetrating trauma where the wound becomes infected.[51] The incubation period from infected wounds varies from 4 to 17 days.[51]

Signs and symptoms consistent with botulism generally develop over several days. Electrodiagnostic study findings are usually similar to those seen in food-borne botulism.[50]

The diagnosis of wound botulism is best made by the isolation of *C botulinum* organisms from the infected abscess. The infected wound should be searched for with care because it may not be obvious. Irrigating the abscess with a sterile saline solution and subsequent culture of the recovered fluid in anaerobic culture media may yield the organism. Unfortunately, the toxin often is not detected in serum, and in wound botulism, the toxin is never found in stool.

The treatment of wound botulism includes debridement of the abscess or infected wound. Penicillin should be administered along with the botulinum antitoxin. Patients should be placed in intensive care and given supportive care, including endotracheal intubation and mechanical ventilation if necessary.

Botulinum A Toxin as a Medication

As the mechanism of action of the botulinum toxin became better understood, it was recognized that the toxin could be used selectively to paralyze muscles.[52] Purified type A botulinum toxin is now used to treat various neurologic disorders including blepharospasm, spasmodic torticollis, hemifacial spasm, strabismus, and laryngeal dystonia or spastic dysphonia.[53-55] The dystonic or spasmodic neurologic illnesses are characterized by involuntary intermittent or sustained contractures of specific groups of muscles. They have been difficult to treat with other medications because the dosage required for any symptomatic relief usually weakens all muscles.

The administration of minute amounts of botulinal toxin into specific skeletal muscles causes localized muscle weakness or paralysis by blocking acetylcholine release at the neuromuscular junctions of only the treated muscles. In addition, there is a diminution of the dystonia or tonic muscle spasms. Botulinal toxin treatment of these facial or neck muscle disorders has given dramatic, albeit temporary, symptomatic relief to thousands of patients. Botulinal toxin treatment usually gives relief for 4 to 12 months before the condition returns. At that time, the botulinal toxin is often readministered to the same muscles. Repeated muscle injections may provide relief for shorter periods than the initial administration. It is not yet clear if botulinal toxin can be readministered indefinitely or whether the effectiveness eventually wears off.

Care must be taken when the toxin is administered because it can diffuse from the inoculation site through tissue to paralyze neuromuscular junctions of adjacent muscles, caus-

ing unwanted side effects such as muscle weakness and dysphagia. In addition, occasionally antibodies against the toxin have developed in patients receiving large doses of the toxin, and these patients do not benefit from repeated toxin injections.[56]

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Articles

Homeless Families and Their Children's Health Problems
A Utah Urban Experience

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Descriptive information was obtained about homeless families in the Intermountain West and their children's health care needs were defined to help professionals develop programs tailored to meet the unique needs of this population. We collected data during the well-child visits of 306 children in 161 families living at the Travelers Aid Society family shelter. The results reveal 2 types of homeless families, episodic and long term. Each requires different levels of assistance. This study's profile of mobile, predominantly white, 2-parent families with few children (mean of 1.2) differs considerably from that of studies conducted on the East and West coasts. The families' nomadic life-style (73.1% came from 32 states other than Utah) present important public health issues, especially because of the recent resurgence of tuberculosis and declining levels of childhood immunizations. The children's health problems were similar to those reported nationally: delayed immunizations, dental decay, anemia, and impaired vision.

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Families, especially with single parents, represent 34% of the total homeless population.[1] Recent reports from Los Angeles, California, however, suggest that this percentage may be somewhat underestimated. About 40% of the Los Angeles homeless population of 40,000 to 50,000 consists of family members.[2] Estimates from New York City suggest that 40% to 45% of its homeless population includes families.[3] These figures represent a dramatic shift in the composition of homelessness in the past decade from single men to families.[4(p17),5]

Homeless families have been characterized as being predominantly female-headed, single-parent families with two to three children, most of whom are preschoolers.[1,5-8] Many investigators describe the homeless families living in Boston, Massachusetts, New York City, and the Los Angeles area as being made up of racial minorities headed by single mothers.[2,6,8]

Researchers speculate that homeless people are at greater risk for poor health than housed persons due to inconsistent and crowded living conditions, poor nutrition, and limited access to adequate health care services.[1,5,9] For homeless children, the main health concerns identified in the literature are ear and upper respiratory tract infections, delayed immunizations, anemia, developmental delay, and dental problems.[3-5,8,9] Homeless children are likely to have twice as many of these disorders as their domiciled peers.[9] Bass and co-workers also point out the prevalence of enteric infections in shelters and the concomitant risk for such infections in young children.[7] Drug-resistant strains of tuberculosis are also appearing in the homeless community. This presents a grave concern for neonates who, after leaving a hospital, may spend their first months in a shelter.[7]

A similar rise in number and proportion of homeless families has been noted in the Intermountain West. Denver, Colorado, and Salt Lake City, Utah, serve most homeless families in this region. Yet, little is known about the experiences of these families. Much of the knowledge that has been gained concerning homelessness has come from the East and West coasts, with a limited focus on other areas of the United States. The purpose of this research, therefore, was to describe the health care needs of homeless children to help health care professionals in the Intermountain West to develop health care programs designed to better meet the needs of this population.

Homeless Families in Salt Lake City

Discrepancies in the reported number of homeless people that are typical throughout the United States are also noted in Salt Lake City. For example, Utah Issues, a nonprofit advocacy group, reports that on any given day there are 4,300 homeless people in Utah, of whom about 80% are in Salt Lake City (population 168,000). Of this number, an estimated 30% to 35% are families with children.* In contrast, a local children's advocacy group, Utah Children, suggests that in 1991 there were 4,635 homeless children in Utah (Utah State Office of Education).

Salt Lake City has one family shelter, operated by Travelers Aid Society (TAS), which houses 29 families with about 60 children on any given day. Three smaller shelters for single mothers and their children serve a combined total of 15 families. The TAS family shelter frequently has a list of 20 families awaiting rooms, many of whom are currently residing at another shelter. An unknown number of homeless

*Utah's 1990 Comprehensive Homeless Assistance Plan, prepared by the Utah State Ad Hoc Homeless Planning Committee and Community Development Division of the Department of Community and Economic Development.

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ABBREVIATIONS USED IN TEXT

AFDC = Aid to Families With Dependent Children
TAS = Travelers Aid Society

families live in local motels or in their cars or "double up" with friends until a room opens up in the family shelter. A pattern of moving in and out of homelessness is evident with many families in the Salt Lake area. For instance, families may live in one or more shelters until their allotted time runs out. They might then move to a motel for a few weeks, leave town or disappear from the shelter system, only to return within a short time to repeat the cycle.

Travelers Aid Society provides space within its family shelter for the Wasatch Homeless Health Care Program. This program manages a medical clinic that serves all sheltered and nonsheltered homeless persons in the city. Because many of the homeless people in Salt Lake City obtain medical care only during acute illnesses, the shelter clinic's original focus of care was episodic in nature. It was recognized that a preventive health care component, particularly for children, was needed. Thus, in June 1989, a comprehensive pediatric program was initiated by the Homeless Children's Health Promotion Program. This program was designed to refocus the crisis-management style of solving health care problems by homeless families toward one of preventing illness. The assumption was that the homeless children in Salt Lake City had untreated health care problems and that they would benefit from readily available health care services.

Purpose of Study

In conjunction with providing preventive health care services for homeless children, data were collected to gain insight into the characteristics of homeless families that could potentially direct the focus of the program. Few preventive health care services for or information about the health care needs of homeless children in the Intermountain West exist. The following research questions served to guide this descriptive study:

- What are the characteristics of the homeless families in Salt Lake City, and do they mirror those of homeless families in other parts of the country?
- What are the major untreated health care problems of the presumably "well" homeless children in Salt Lake City?

Methods

In 1989, once the Pediatric Health Promotion Program was operational, the TAS family shelter implemented a policy requiring all children to have well-child-care examinations within the first week of their stay. The well-child visit consists of a family interview, a complete physical examination of all the children, health education, and needed immunizations. Of the approximately 500 children who resided at the shelter during the period of June 1, 1989, to May 30, 1990, 306 (61.2%) were examined by a pediatric nurse practitioner who was employed part-time to develop the program. She interviewed 161 families and examined their children. Appointments for children who missed their first scheduled appointments were rescheduled, and a reminder was taped on the family's door. Because of staffing limitations, it was not possible to follow up on the families who missed their rescheduled appointments.

Approach to Data Collection

The data were collected during the well-child-care visits as part of the routine intake process for new families. The interview and examination form that was developed for this program included demographic information about the families, well-child screening, and laboratory results, and served as the permanent document for each child's chart. The federal Medicaid Early Periodic Screening and Diagnostic Testing form was used to standardize the examinations. Diagnoses were identified using the International Classification of Diseases codes.[10]

The practitioner interviewed the parent(s) while the children were being measured or tested by an assistant. Included in the demographic information were questions regarding the parent's age, educational level, place of residence before the TAS family shelter, and in what state or country they had last resided for six months or longer. The child's height, weight, and head circumference (if younger than 2 years) were recorded and plotted on an age- and sex-appropriate growth grid. A finger-stick blood specimen was drawn for a hematocrit level on all children 6 months of age or older. Hematocrit standards developed by the federally funded Special Supplemental Food Program for Women, Infants, and Children were used to determine the presence of anemia. Vision screening was done on children who were 4 years of age or older. The Snellen illiterate "E" vision acuity test and its standards were used to check for visual impairment. Blood pressure was taken on children aged 3 years and older. A urine specimen was collected if the child was 2 years of age or older and cooperative. Because of cost and staffing constraints, stool specimens for culture, ova, and parasites were collected on symptomatic children only. Parents answered questions regarding family composition, past and current medical status, and current health of their children. The presence of dental caries was recorded when the practitioner could visually identify tooth decay during the examination. A Denver Developmental Screening Test was done if the nurse practitioner had reason to suspect developmental delays based on her interaction with the parent and child or if a shelter caseworker had concerns about a particular child.[11]

Acute illnesses were treated during the visit. Immunizations were updated and tuberculin skin tests (purified protein derivative) placed. Delayed immunizations were defined as not being current with immunizations appropriate for a child's age according to the recommended schedule of the American Academy of Pediatrics.[12]

Data Analysis

The interview and examination information was routinely collected and placed into a computerized data base specifically designed for this project. These data were then collectively transferred to a data file that could be statistically analyzed using the Statistical Package for the Social Sciences. Statistical analyses of these data focused on the demographic characteristics of the homeless families in general and the health care needs of the children in particular.

Results

Family Demographics

Tables 1 and 2 summarize the demographic characteristics of the 161 families. More than half the families had both parents (57.8%). Single-mother families comprised 32.3%

of the sample. Unlike the racial or ethnic makeup of other major metropolitan areas, the homeless children in this study were predominantly white (62.1%) or multiracial (15.0%), with 10.8% American Indian, 6.2% Hispanic or Mexican, and 5.9% African American. Ethnicity was based on the entire sample of 306 children, since many children within the same family unit had different fathers.

TABLE 1.—*Demographic Characteristics of Sheltered Homeless Families Living in Salt Lake City, Utah, June 1, 1989, to May 30, 1990*

Characteristic	Sample, No.	Mean	Median	SD	Range
Age, yr					
Mother	147	29.5	29.0	7.7	15 to 59
Father	106	32.2	30.5	8.0	18 to 61
Child	306	6.2	5.5	4.5	2 wk to 18
No. of children in family	161	1.2	1.0	1.4	1 to 6
No. of days homeless	161	49.9	14.0	97.5	1 to 730
Education levels attained, yr					
Mother	147	11.2	12.0	1.9	2 to 17
Father	106	10.8	12.0	2.0	3 to 16

TABLE 2.—*Family Composition, Ethnicity, and Federal Aid Status of the Homeless Families Living in Salt Lake City, Utah*

Characteristic	Homeless Families No.	Homeless Families %
Family unit (n = 161)		
2 Parents	93	57.8
Single mother	52	32.3
Single father	13	8.1
Parent with friend	2	1.2
With guardian	1	0.6
Race of children (n = 306)		
White	190	62.1
Multiracial	46	15.0
American Indian	33	10.8
Hispanic	19	6.2
African American	18	5.9
Benefit status of family		
Food stamps	64	40.0
WIC	55	34.2

WIC = Women, Infants, and Children nutrition program

The average age of the parents in this study was similar to what has been reported in the literature: mothers, 29.5 years old; fathers, 32.2 years.[2,5] The children's mean age was 6.2 years, again similar to other reports.[5,13] The average family size, however, was smaller than what has been cited previously, with the average number of children per family being only 1.2.[2,4,8,13]

The range of educational levels for fathers and mothers was wide (2 to 17 years). Nearly half of the mothers (45.8%) and fathers (47.6%) had fewer than 12 years of education. Of the 157 school-aged children, 51 (32.5%) were in an incorrect grade for their age.

Parents were also asked to identify the state (or country) in which they had last resided for six months or longer. For example, if a family left Florida where they had lived for seven months and then traveled to Texas and stayed there for two weeks, moved on to Nevada for a month, and ended up in Salt Lake City, their last permanent residence was recorded as Florida. They were then considered to have been homeless for three months at the time of their entry into the TAS family shelter. Figure 1 shows that only 26.9% of the families housed at the shelter throughout the study period originated from Utah, with the remainder (73.1%) traveling to Salt Lake City from 32 other states and Honduras. Many of the families had originated from the West Coast or neighboring Intermountain West states: California, 15.0%; Arizona, 5.6%; Nevada, 5.0%; and Idaho, 4.4%.

The family's entitlement status indicated the financial support the parents were receiving at the time of their child's clinic visit. Only 36.2% of the families were receiving Aid to Families With Dependent Children (AFDC) or Medicaid benefits when they entered the shelter. Of the 161 families, 40.0% were receiving food stamps, and 5% were receiving social security benefits. One single father had private insurance at the time of his children's clinic visit.

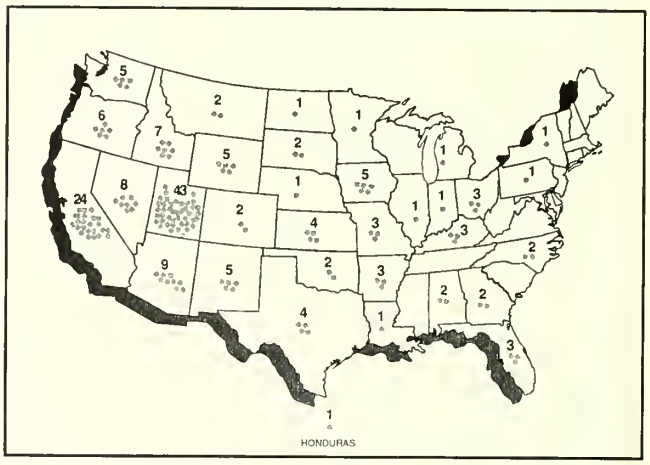

Figure 1.—The map shows the last state (plus Honduras) each family lived for 6 months or longer (n = 161; 3 families were excluded from the data analysis because of incomplete information).

Children's Health Problems

The children in this study were presumably well children. If a child was sick, the parent(s) brought the child into the clinic for episodic care, and the well-child-care visit was rescheduled. Table 3 outlines the major health care issues identified during the well-child examinations.

The results of this study indicate that many of the homeless children were in need of routine preventive health care services. At least one health care problem was identified in 237 (77%) of the 306 children. The seven most frequent concerns included delayed immunizations, visible dental caries, anemia, impaired vision, diaper rash, otitis media, and head lice. Untreated acute problems such as otitis media, upper respiratory tract illnesses, and diarrhea were also diagnosed and treated during the well-child examinations.

Of the group of 166 children who were between 2 months and 6 years of age, 4.8% were developmentally delayed in one or more areas according to the Denver Developmental Screening Test. Of the parents whose children had health care problems, 30% were not aware that their child had an illness or disability that required treatment. In all, 70% of them revealed that they knew such a problem existed but that they either did not have sufficient funds to do anything about it or they had moved and did not follow through with the recommended treatment.

Discussion

The results of this study suggest that the characteristics of homeless families differ dramatically from one part of the country to another. Understanding these differences is necessary when developing services to meet the health care needs of homeless children in the various regions of the United States.

Geographic and Ethnic Issues

The predominance of white children in the Utah homeless population might be explained by Utah's ethnic makeup: 93.8% white (US Bureau of the Census, 1990). Yet, most of the families in the sample were not from Utah but rather had traveled from other areas. Although the reasons why more homeless white and multiracial families migrate to and through Utah was not a primary focus of this study, there are several possible reasons for this phenomenon.

The mere geographic location of Salt Lake City midway between the cities of Denver, Colorado, Reno, Nevada, Boise, Idaho, and Las Vegas, Nevada, may have influenced the composition of the flow of families into Utah. Salt Lake City is considered a transportation crossroads. Many families revealed that they were traveling to another destination (California, for instance) when they ran out of money or their car broke down. Others had heard of Utah's relatively strong economy and low crime rates compared with other states.

A possible explanation for the limited number of homeless Utahns—only 26.8% of the homeless families had lived in Utah for six months or longer—is that nearly 70% of Utah residents are members of the Church of Jesus Christ of Latter-Day Saints (Mormon). The Mormon Church has a comprehensive welfare system to assist its families with housing and food problems, thus helping such families avoid homelessness.

TABLE 3.—*Health Problems Discovered During Well-Child-Care Clinics*

Type of Problems (age range for procedure)	*Children, No.**	*Cases*	
		No.	*%†*
Delayed immunizations (2 mo to 18 yr)	296	121	40.9
Visible dental caries (2 to 18 yr)	245	82	27.7
Anemia (6 mo to 18 yr)	281	42	15.0
Candidal diaper rash (newborn to 2 yr)	57	8	14.8
Impaired vision	188	26	13.8
Otitis media	306	33	10.8
Lice infestation	306	31	10.1
Viral respiratory illness	306	20	6.5
Failure to thrive (newborn to 2 yr)	57	3	5.3
Dental anomalies (4 to 18 yr)	188	9	4.8
Developmental delay (2 mo to 6 yr)	166	8	4.8
Speech delay (4 to 18 yr)	188	8	4.3
Genitourinary problem	306	9	2.9
Enuresis (4 to 18 yr)	188	5	2.6
Heart murmur	306	6	2.0
Obesity	306	6	2.0
Scoliosis	306	6	2.0
Unspecified skin rash	306	3	0.7
Asthma	306	2	0.6

*Number changes because of age-appropriate types of screening.
†Percentage of children within age-appropriate groups.

It could be speculated that the relatively large percentage of American Indian families (10.8%) traveled to Salt Lake City from reservations in the Four Corners area of Utah, Nevada, Arizona, and Colorado during the migrant farming season. Others may have been in search of more permanent work and living arrangements. The noticeably low percentage of African-American families (5.9%) in this sample may reflect their preference for more culturally diverse communities.

Life-style Patterns

Two-parent families comprised 57.8% of the sample in this study. The sample may be skewed because the clinic is located within a family shelter. Many of the female-headed families, however, regularly moved from the two smaller single-women shelters to the family shelter when room became available. Therefore, many of these single mothers would have been included in this study. In addition, there are few shelters in the Intermountain West that serve two-parent families. The TAS family shelter may well house a larger than average number of two-parent families.

The wide range (1 to 730 days) of "number of days homeless" indicates that there were at least two types of homeless families within this sample: episodic (median, 14 days) and long term (mean, 49.9). These two groups present with different issues and medical needs. Of particular concern are the families who have been homeless a long time who return to the emergency shelters year after year. With each return, the parents appear more depressed and their children seem more streetwise and hardened. Once a family reaches this lowest level of poverty and despair, it takes great time and energy for them to regroup and reenter their communities.

Another noteworthy family characteristic was that the majority of families in this study were not long-term welfare recipients. Although many families later received benefits, less than a quarter of them reported receiving AFDC or Social Security Insurance at the time of the intake interview. Many of the two-parent families may represent a segment of the working poor who were unable to succeed in their communities and left in search of work and more affordable housing.

Studies examining whether homeless children are more vulnerable to communicable diseases such as diphtheria, measles, tuberculosis, or poliomyelitis do not currently exist. Yet, epidemiologic data suggest that these children are a high-risk group for contracting and spreading such illnesses.[3] It is not known if the geographic mobility of these homeless families places their children at a greater health risk to the general population, but the transient and communal nature of their living arrangements is a potential public health concern.[5] Recent outbreaks of tuberculosis in communal settings may soon convince communities to take a closer look at their shelters, the risk factors that exist within their systems, and homeless children's immunization levels. The high percentage of children with delayed immunizations found in this study may partially reflect the record-keeping practices of the families who had forgotten where or what shots their children had received in other states.

Almost half of the parents, nearly all of whom were in their late 20s to early 30s, had not finished high school. This pattern of not completing an educational program reemerges in the context of their children's education, with almost a third of the children being in an incorrect grade for their age. The reasons usually given for school delays were that the children had been held back because of poor school perfor-

mance or the family had moved into another school district, which necessitated repeating a grade. This information is consistent with studies that suggest that between 30% and 50% of homeless children have, at some point, repeated a grade.[1,5,9] For housed children, the primary reason for school absenteeism is illness. For homeless children the major reason is family transience.[14]

A mobile life-style creates unforeseen problems in obtaining governmental assistance and in entering new school districts. Most state assistance programs and public schools require identification from their applicants such as birth certificates, Social Security numbers, or immunization records. The clients seen at the TAS family shelter often experienced delays in receiving welfare benefits and frequently had to restart their children's immunization series because the families had left their last residence without gathering essential documents.

Homeless Children's Health Concerns

The children in this study, similar to homeless children in other parts of the country, were poorly immunized, had dental decay, anemia, lice, and untreated acute infections. The families' inconsistent diets, cramped living quarters, and difficulty in managing basic hygiene while on the road undoubtedly contributed to these health problems.

Of the health problems identified during the well-child examinations, 17% were treated, which deferred a number of visits to the local hospital departments for minor acute care. Children with chronic health problems were referred to the local pediatric hospital, Primary Children's Medical Center. The liaison between the shelter clinic and the medical center made it possible to schedule the children into specialty clinics within a week. If a child was not eligible for Medicaid, the hospital's charity fund covered the cost of the specialty clinic visit.

Many children benefited from the mandatory screening done at the on-site shelter medical clinic. For example, a 17-year-old boy was found to have an undescended testicle. He also had severe dental caries and needed glasses. While his family stayed at the emergency shelter, he had surgery, had his cavities filled, and was fitted for glasses. Another child with learning difficulties was found to have a vision problem. A toddler had recurrent ear infections and as a consequence was referred to the Primary Children's Medical Center for a tympanostomy with tubes inserted.

There are several limitations to this study that suggest that the health care needs of the children who participated in this project may be underestimated. Because of limited staff, only 61.2% of the children who were in shelter participated in the screening program. It is suggested that the children who were seen were probably from the more stable homeless families who understood the shelter policy and followed through with their appointments.

It is also known that the brief observation of a child during a clinic visit is not a sensitive screening tool for developmental delay. Because of limited resources during the initiation of the program, it was the only method available to the practitioner considering the multitude of health care needs of the population. An additional factor that also needs to be considered is the type of homeless families (episodic or long term) encountered during a study of developmental delay and how the duration of homelessness affects a child's development.

Recommendations for Future Research and Program Development

Data Collection

Gathering psychosocial and demographic information during a clinic visit made it difficult to elicit the reasons why homeless families travel to and through Utah. Obtaining such information during clinical visits, however, improves the quality of a program by having a built-in assessment and evaluation tool. Standardizing data collection tools would aid in doing cross-comparison studies in various regions.

Program Development

Educating referral agencies about the plight of homeless people facilitates the rapid entry of the homeless into community-based health care facilities. Increased flexibility in rescheduling appointments, shorter waiting times, and a staff that is sensitive to the needs of homeless families make referral follow-through more likely. Our experience has been that a close liaison with a hospital outpatient clinic is key to securing specialty appointments and covering the cost of children not eligible for Medicaid.

With an understanding of the unique needs of homeless families, alternative methods of offering health care services can be developed. For example, with informed parental consent, vision, dental, and hearing screening services can be offered through the clinic while the parents are with their caseworkers.

Working closely with shelter caseworkers improves follow-through with specialty health care appointments. Shelter caseworkers, following a case-management model to provide services, are able to put the children's health care needs in perspective. They are more likely to know the broader concerns the parents face regarding employment and housing. A shelter policy requiring that all children receive well-child care makes it possible to track immunization levels and to monitor the health status of the entire shelter.

Obstacles that limit access to health care such as language, cost, transportation, and day care can be identified during the well-child-care visits and circumvented by shelter caseworkers with the help of the clinic staff. For example, taxi vouchers are given to families who have referral appointments to off-site clinics. Day-care services are obtained for siblings. Medicaid or other charity services are used to defer the cost of treatment.

Community Awareness

A strong community network has a twofold effect. It helps a shelter-based health care program draw on available resources, which improves the overall delivery of health care to underserved children and educates the greater community regarding the needs of its homeless population. For example, involving health-related educational institutions enhances a program's volunteer efforts and raises the social consciousness of future leaders in the community.

It is important that all professionals who care for homeless children in various departments of a hospital take the opportunity to update immunizations and educate families regarding record keeping and the need for consistent health care. Emergency department physicians, in particular, may be the only professionals a homeless child visits during infancy. Updating immunizations and providing resource information are, therefore, key components of intervention for homeless families.

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* * *

GOLD FILLING

My dentist says,
"Do you ever use
a computer
to write poetry?

If you find a phrase
you like you
can save it,

Like 'blue sky',
for instance,
or 'brown mud'."

I think,
"Do you ever fill
a tooth by
walkie-talkie?

If you find a tooth
you like you
can save it.

Craft requires
your hands in
my mouth."

JAN HENSON DOW©
Danbury, Connecticut

Articles

Controversies in Measles Immunization Recommendations

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Controversy in medicine is inevitable, but it becomes problematic when the issue is a serious public health problem requiring a clear plan of action. In recent years measles has made a major resurgence in this country, with provisional figures showing 89 measles-related deaths in 1990. The Immunization Practices Advisory Committee of the US Public Health Service, the Committee on Infectious Diseases of the American Academy of Pediatrics, and the US Preventive Services Task Force have all issued recommendations for measles immunization. Most of these recommendations are in agreement, but they conflict on the age at which vaccination should be given and the number of doses. To assist physicians in disentangling this complex web, I review the history of measles immunization in the United States and give the rationale for particular positions wherein the groups disagree. I describe protocols for routine vaccinations, endemic areas, outbreak control, colleges and universities, and international travel.

(Robbins AS: Controversies in measles immunization recommendations. West J Med 1993 Jan; 158:36-39)

In setting the national disease prevention goals for the year 2000, the United States Public Health Service listed as one of its objectives the elimination of measles, stating that "measles in the United States is an example of an infectious disease problem that should be readily controlled in that a vaccine has been available since 1963."[1] Indeed, since the introduction of an effective vaccine, the number of measles cases in this country has dropped by 99%, reaching an all-time low of 1,497 cases in 1983.[2] But in 1989 an epidemic of 18,193 cases was reported,[3] and the 1990 total of 27,786 cases represents the highest incidence since 1977.[4] The provisional 1990 total of 89 measles-related deaths is the highest reported since 1971 (William Atkinson, MD, Division of Immunization, Centers for Disease Control, oral communication, December 1992). Controversy exists as to why this resurgence has occurred, with some emphasizing inadequate immunization, especially among inner-city children,[5,6] and others, also lamenting poor compliance with vaccination protocols, pointing to the additional issue of vaccine failure.[2]

Measles in the United States is far from controlled, despite much advice from experts on how to accomplish this. In fact, the advice is so plentiful as to make it difficult to remember which agencies or committees advise which strategies, and, in some cases, the recommendations of different groups disagree sharply. This is unfortunate because if ever a public health problem demanded a clear plan of attack, it is the control of measles transmission in the United States. In this article I review the recommendations for measles prevention and control that have been put forth by three influential groups: the Immunization Practices Advisory Committee (ACIP) of the US Public Health Service, the Committee on Infectious Diseases of the American Academy of Pediatrics (AAP), and the US Preventive Services Task Force (USPSTF). I will focus on the recommendations concerning immunization, mainly involving efforts directed toward children.

It should be remembered that the audiences addressed by these groups differ somewhat. The ACIP is charged with assisting the formulation of federal immunization policy guiding public sector pediatricians. The recommendations of the AAP are directed more specifically to private sector pediatricians. And while the authors of the USPSTF report write mainly for primary care physicians, they offer their recommendations to a wider audience, including policymakers, researchers, and those responsible for the financing of health care.

A specific issue on which all three groups agree is that, after the first birthday, the vaccine used to immunize against measles should be the live measles, mumps, and rubella virus vaccine (MMR). The ACIP and AAP recommendations are based in their routine two-dose measles vaccination schedule. They point out the need for mumps revaccination, since mumps outbreaks can occur in highly vaccinated populations[2,7,8]; the rubella revaccination that occurs with the second administration of MMR is simply a safeguard against rubella vaccine failure, although this has not been a notable problem.[2] The three groups also agree that for children younger than 1 year, the monovalent measles vaccine should be used instead of MMR or the live measles and rubella virus vaccine. Finally, all three groups agree that, under normal circumstances in nonendemic areas, MMR should be administered routinely at 15 months of age.[2,8,9]

In contrasting the positions of these groups, I discuss their recommendations on the age(s) and number of doses for routine circumstances and endemic areas; protocols for epidemics; and special protocols for colleges, health care settings, and international travel.

Routine Circumstances

As a prologue to examining current controversies, it is interesting to look at the history of measles immunization recommendations in the United States. In 1965 the ACIP recommended routine measles immunization for all infants beginning at 12 months of age. In 1976 the ACIP changed the recommended age at vaccination to 15 months because clinical research had shown substantially higher vaccine failure

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ABBREVIATIONS USED IN TEXT

AAP = [Committee on Infectious Diseases of the] American Academy of Pediatrics
ACIP = Immunization Practices Advisory Committee [US Public Health Service]
MMR = measles-mumps-rubella [vaccine]
USPSTF = US Preventive Services Task Force

rates in children immunized at 12 months compared with those vaccinated later. Subsequent studies have found 95% seroconversion rates in infants receiving the vaccine at 15 months[10]; in most cases, the immunity conferred by seroconversion is long term, probably lifelong.[11] Then in 1989, in an effort to prevent measles in the 5% of infants and children not seroconverting after immunization (primary vaccine failures), both the ACIP and the AAP announced they were modifying their protocols to include two doses of vaccine under routine circumstances. Although the ACIP and the AAP agree that two doses of MMR should be given, they do not agree on when this should be done, and the USPSTF does not concur in this issue, recommending instead a single-dose routine immunization protocol (vaccine at 15 months of age), only adding a second dose routinely in areas endemic for measles (Table 1).[2,8,9]

The feasibility of implementation is the major impetus behind the ACIP school-entry recommendation. Vaccination with diphtheria and tetanus toxoids and pertussis vaccine adsorbed and oral poliovirus vaccine between 4 and 6 years of age is already part of the current childhood immunization schedule and mandated by school districts for entry to kindergarten or first grade. Moreover, most schools have well-established systems in place to identify and track children who have not received the required immunizations. The ACIP protocol has the drawback that, in a given community, it requires a long time interval for full effects, given the fact that most measles outbreaks among vaccinated persons occur in the 12- to 18-year-old age group.[12]

In contrast, the AAP recommendation for a second dose at middle school or junior high school entry is based on its rapid effects; giving vaccine to 11- to 12-year-olds would substantially decrease the incidence of outbreaks among primary vaccine failures almost immediately. A vaccination program among children at this age would be difficult to implement, however, especially among poor inner-city populations, contrary to the AAP assertion that "[v]accination at this age can easily be accomplished within the existing recommendations for health maintenance visits."[8,13]

Endemic Areas

On the issue of immunization in endemic areas, the ACIP and AAP recommendations are in complete agreement; again, the USPSTF stands alone. All, however, agree on at least one criterion for an endemic area: a county or city reporting more than five cases among preschool-aged children during each of the previous five years. Both the ACIP and AAP add two further criteria: a county with a recent outbreak among unvaccinated preschool-aged children; and a county with a large inner-city urban population (the AAP words this slightly differently, as "cities with large unvaccinated populations," which, by recent reports, constitutes almost all large cities[14] and is especially a problem among the African-American and Hispanic children living in such cities[15]).

The ACIP and AAP concur in recommending to lower the age at the first dose of MMR from 15 months to 12 months. This recommendation is informed by epidemiologic studies showing that in some outbreaks as many as 40% of cases occurred in children younger than 16 months of age.[16] In sharp contrast, the USPSTF does not recommend vaccination at 12 months for endemic areas; instead, it proposes the usual dose of MMR at 15 months and in addition a dose of monovalent measles vaccine at 9 months of age. This is the only circumstance in which the USPSTF recommends a two-dose protocol.

Outbreak Control

During a measles epidemic the need for a clear-cut protocol is urgent. It is fortunate in this regard that the recommendations put forth by the ACIP and AAP on outbreak control are again in complete agreement. The ACIP and AAP make recommendations concerning school-based outbreaks, outbreaks among preschool-aged children, and outbreaks in medical settings (Table 2).

Both the ACIP and AAP state categorically that after "at risk" persons are revaccinated, and after previously unvaccinated persons receive their first dose of MMR as part of the outbreak control program, they may immediately be readmitted to school. Some have called for a modification of this last point in the recommendations, pointing out that the evidence for a protective effect of MMR administered to susceptible persons as postexposure prophylaxis is stronger when it is given within the first 72 hours after exposure.[17-21] The level of protective effect in those receiving MMR prophylaxis more than 72 hours after exposure was disappointingly low in a 1989 school-based outbreak in the state of Washington; the

TABLE 1.—*Recommendations for Measles-Mumps-Rubella (MMR) Vaccination for Routine Circumstances, Endemic Areas, and Institutions of Higher Learning*

Measles Circumstance	*Vaccination Recommendations*		
	ACIP	*AAP*	*USPSTF*
Routine	2 doses of MMR: 1st at 15 mo, 2nd at school entry (4 to 6 yr)	2 doses of MMR: 1st at 15 mo, 2nd at junior high entry (11 to 12 yr)	Single dose of MMR at 15 mo
Endemic areas*	2 doses of MMR: 1st at 12 mo, 2nd at school entry (4 to 6 yr)	2 doses of MMR: 1st at 12 mo, 2nd at school entry (4 to 6 yr)	2 doses of vaccine: 1st with monovalent measles at 9 mo; 2nd with MMR at 15 mo
Colleges and other institutions of higher learning	Dose of MMR on entry if unable to furnish proper documentation†	Same as ACIP	No specific recommendations

AAP = American Academy of Pediatrics, ACIP = Immunization Practices Advisory Committee, USPSTF = US Preventive Services Task Force

*A county or city reporting >5 cases among preschool-aged children during each of the previous 5 years; a county with a recent outbreak among unvaccinated preschool-aged children; or a county with a large inner-city urban population.

†A history of physician-diagnosed measles; laboratory proof of immunity; or proof of receipt of 2 doses of measles vaccine.

TABLE 2.—*Recommendations for Measles-Mumps-Rubella (MMR) Vaccination for Outbreak Control and International Travel*

Measles Circumstance	*Vaccination Recommendations*		
	ACIP	*AAP*	*USPSTF*
Outbreaks in preschool-aged groups	Monovalent vaccine* for infants as young as 6 mo; revaccinate with MMR at 15 mo and at school entry	Monovalent vaccine for infants as young as 6 mo; revaccinate with MMR at 15 mo and at junior high entry	No specific recommendations
School-based outbreaks	Dose of MMR for all "at risk"† students, siblings, and school personnel	Same as ACIP	No specific recommendations
Outbreaks in medical settings	Dose of MMR for all "at risk"† employees with direct patient contact	Same as ACIP	No specific recommendations
International travel	Dose of MMR for any travelers who cannot furnish proper documentation†	Same as ACIP	No specific recommendations

AAP = American Academy of Pediatrics, ACIP = Immunization Practices Advisory Committee, USPSTF = US Preventive Services Task Force

*The MMR vaccine may be used if monovalent vaccine unavailable.
†Those born in or after 1957 who cannot provide documentation that they received 2 doses of measles vaccine on or after their first birthday or other evidence of measles immunity.

school district adopted a readmission policy in which persons who were vaccinated within 72 hours after exposure were immediately readmitted to school, whereas those vaccinated after 72 hours were excluded for 14 days.[22]

Colleges and Other Higher Education Institutions

Both the ACIP and AAP recommendations address the issue of measles immunization among college and university students because, particularly in 1989, a number of outbreaks occurred on college campuses (Table 1). The USPSTF report is silent on this issue.

International Travelers

Both the ACIP and AAP recommendations state categorically that persons traveling abroad should be immune to measles. (The USPSTF does not speak to this issue.) The AAP report points out that an increasing number of measles cases seen in the US are actually attributable to exposure in foreign countries.

Both groups also emphasize the importance of proper immunization for children traveling to areas where measles is endemic or epidemic. For children traveling to such locations, the dose for initial vaccination should be lowered to 12 months of age; children 12 to 14 months old should have a dose of MMR before departure. Those 6 to 11 months of age should be given monovalent measles vaccine before departure (MMR can be used if monovalent vaccine is unavailable). If a child who received a vaccination before age 1 year remains in an area that is endemic or epidemic for measles, she or he should be revaccinated at 12 to 15 months with MMR. If the child returns to the US, revaccination with MMR should be given at the usual age of 15 months. If the child remains abroad, the timing of the second dose of MMR should be either at one of the usual times advised by the ACIP or AAP or according to local policy.

Recommendations for Uniformity

Although there are undoubtedly many causes underlying the recent surge in measles cases in the US, it appears that failure to vaccinate children at the appropriate age is the most important factor, with vaccine failure playing a small role. Perhaps parents, or even health care professionals, are confused about when children need to be immunized. To the extent that members of influential groups like the ACIP, the AAP, and the USPSTF can meet together, discuss the reasons for their differences, and issue a more uniform set of immunization recommendations, the complex task of eliminating measles in the US by the year 2000 will be a simpler one.

Toward this end, I offer the following observations and recommendations. First, it seems the two main issues of contention between the three groups are whether to give one or two doses of MMR routinely and when to give the second dose if one is to be given. In the interest of uniformity, and because measles vaccine failure seems to have accounted for a substantial number of cases among school-aged children and college students, it seems prudent to give a second dose routinely. Moreover, a second dose of MMR is not associated with a substantial risk of injury, as long as it is not given where contraindicated. On the issue of when to give the second dose, the AAP recommendation to administer it on junior high entry, although potentially leading to more rapid results, has been criticized as impractical, particularly in urban centers. If, in fact, the AAP protocol is impractical, the mere theoretical attractiveness of more rapid effects would prove of no value if the second dose is not actually given. Again, in the interest of uniformity, and because the ACIP protocol is more easily implemented, it seems prudent to adopt the school-entry reimmunization recommendation. The mutual goal of the three advisory groups—measles control—would be well served if agreement could be reached on these two main issues.

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* * *

THE SIGN

"What shall be the sign
that the Lord shall heal me?"

II KINGS 20:8

When she heard Hezekiah, king of Judah,
granted fifteen years beyond his sickness,
she asked God for five.

His was a kingdom of sand dunes
stretched west of the Dead Sea,
a falcon-headed land staring east,
with Jerusalem its eye.
To the north, fertile Israel had farms and wealth.
To the west, rich caravans bumped south to Egypt,
skirting rocky Judah
whose only traders were the dry winds.

She has no kingdom to claim,
but a flat house in the Yamhill Valley,
which she cleans and sanctifies
for her husband and children,
and a borrowed field
where she plants strawberries:
durable white-hearted Bentons,
and fragile red-blooded Hoods.

Hezekiah's treatment consisted
of a paste of figs,
prescribed by that ragged clairvoyant,
Isaiah, confidant of angels,
and laid upon his boils.

She lies down in a room alone,
watched through glass by radiologists,
while a cross clipped to her head
buzzes red,
sending to thirty white tumors
a message
beyond the reach of figs.

This was the sign the king sought:
the shadow reverse directions
and the very day
climb back to morning.

But she disdains theatrics:
she's always known
the faithfulness of God
in the natural bend of time.

So she goes about her hoeing
as the shadow darkens sundial
and beyond,
a dark lid over the strawberries
and the narrow stand of oaks along the river.

And she enjoins her family
in her song of thanksgiving:
The living, the living shall praise Thee
as we do this day.

This brief, magnificent day.

MARTHA GIES©
Portland, Oregon

Articles

HIV-1 Seroprevalence Among Women Attending Sexually Transmitted Disease Clinics in California

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To evaluate the distribution of the human immunodeficiency virus type 1 (HIV-1) epidemic among California women, we analyzed HIV-1 seroprevalence and risk factors among women attending sexually transmitted disease (STD) clinics in 21 local health jurisdictions. Using standardized protocols developed by the Centers for Disease Control, we tested unlinked serum specimens from women attending participating STD clinics in 1989. We analyzed demographic characteristics, HIV risk exposure groups, and results of HIV-1 antibody testing on 17,210 specimens with an overall HIV-1 seroprevalence of 0.57%. Seroprevalence rates were highest for African-American women, women 25 to 29 years of age, injection drug users, and women attending STD clinics in San Francisco. After multiple logistic regression analysis, HIV-1 seropositivity remained highest for these four groups. The rate of HIV-1 infection among women attending STD clinics in California underscores the continued need to make HIV counseling and testing an integral component of routine services for women being evaluated for, or presenting with, sexually transmitted diseases.

(Wilson MJ, Marelich WD, Lemp GF, et al: HIV-1 seroprevalence among women attending sexually transmitted disease clinics in California. West J Med 1993 Jan; 158:40-43)

Although most cases of the acquired immunodeficiency syndrome (AIDS) in the United States have occurred among men, women remain at risk for human immunodeficiency virus type 1 (HIV-1) infection through sexual contact and sharing needles with infected partners. Of the 202,921 adults reported with AIDS in the United States through December 1991,[1] 21,225 (10.5%) were women. In California, women accounted for 3.7% (1,460) of the 39,813 adult AIDS cases reported through December 1991.[2] In 1991 alone, 4.9% of all adult cases in California occurred in women. Each year, women account for an increasing percentage of AIDS cases, both in the United States as a whole and in California. However, AIDS case surveillance data do not reflect current trends in HIV infection due to the long incubation period before the development of AIDS-defining conditions.

As part of a statewide effort to evaluate the distribution of the HIV-1 epidemic in California, we examined HIV-1 seroprevalence among women attending sexually transmitted disease (STD) clinics in California during 1989. The distribution of HIV-1 infection among California women is not well defined. More than 6,000 HIV-infected women were estimated to be living in California in 1990.[3] Because of the high morbidity associated with HIV infection and the potential for increased heterosexual and perinatal transmission, we attempted to quantify levels of infection and markers for high-risk behavior in this high-risk population.

As a group, STD clinic patients can be expected to have a higher prevalence of behaviors associated with HIV transmission than the population as a whole. Seroprevalence data among this group of women can provide valuable information on HIV disease surveillance, prevention, and program evaluation.

Methods

Study Population

In 1989, we conducted unlinked HIV-1 seroprevalence surveys at STD clinics in 21 of California's 61 local health jurisdictions using standardized HIV Family of Surveys research protocols developed by the federal Centers for Disease Control (CDC).[4] Public STD clinic sites were chosen based on clinic volume and willingness of the local health jurisdiction to participate in the surveys. Most clinics were located in urban settings, although a third of the participating jurisdictions have substantial rural populations. Protocols were reviewed and approved by the California Health and Welfare Agency Committee for the Protection of Human Subjects. Clients of STD clinics were eligible for the survey on their first visit for a new STD episode or referral. Clients were excluded from the survey if

- They had visited the clinic in the previous 90 days from the date of the current visit;

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CDC = Centers for Disease Control
CI = confidence interval
HIV-1 = human immunodeficiency virus type 1
OR = odds ratio
STD = sexually transmitted disease

- They had come to the clinic specifically for an HIV antibody test; or
- They did not have a blood specimen drawn for syphilis serology.

Eligible specimens were collected consecutively from men and women until at least 500 women attending the clinic during the survey period were sampled. The survey period in 1989 ranged from two months in some clinics to a full year in others, depending on clinic volume. Because of the unlinked study design, it is possible that a patient with several new STD episodes could be included more than once in the sample. A total of 52,228 serum specimens were tested from January 1989 through December 1989. Of these, 17,221 (33%) were from women.

Laboratory Methods

Serum specimens were tested first by local public health laboratories using enzyme immunoassay for HIV-1 antibody.[5] Nonreactive specimens were reported as negative. Repeatedly reactive specimens were tested by Western blot assay for the presence of HIV-1–specific bands. Results from repeatedly reactive specimens were reported as positive, negative, or indeterminate on the basis of Western blot results using CDC Public Health Service criteria.[6]

Descriptive Variables

Race or ethnicity, five-year age groupings, county of clinic location, and HIV risk-exposure information from client questionnaires were collected on a standardized CDC data collection form completed by clinic personnel at intake.[4] Information on HIV risk exposure included sexual orientation, injection drug use, and sexual partner of persons at risk for HIV (such as female sexual partner of bisexual man, sexual partner of person with HIV or AIDS, and sexual partner of injection drug user). Women whose data collection forms were marked "heterosexual" only were included in the group "sex with person of unknown risk." Women with no risk exposure information were included in the "undetermined risk" group. Information about crack cocaine use and trading sex for drugs was not routinely collected. To characterize regional differences in prevalence rates, clinic locations were aggregated into eight single- or multicounty geographic regions: Central Coast (Monterey, Santa Barbara, Santa Cruz), Northern Valley (El Dorado, Sacramento, Solano), Central Valley (Fresno, Kern, San Joaquin), Southern Valley (Orange, San Bernardino), San Diego, Los Angeles, Bay Area (Alameda, Contra Costa, Marin, San Mateo, Santa Clara), and San Francisco. Counties that were aggregated into regions had similar HIV seroprevalence rates for women and contiguous geographic boundaries.

Data Analysis

Rates of HIV-1 seroprevalence and 95% confidence intervals were calculated for race or ethnicity, region, age grouping, and HIV risk-exposure group.[7] Odds ratios were calculated to measure associations between HIV-1 infection and levels of the descriptive variables.[8] Because odds ratios cannot be calculated reliably for categories with zero seropositives,[7] and because adding an arbitrary constant to cells may greatly overestimate true odds for subgroups with small sample sizes, cases reporting Asian or Pacific Islander, other, and undetermined race or ethnicity and cases reporting undetermined age were removed from subsequent analyses.[9]

Multiple logistic regression analyses were undertaken to simultaneously account for the effects of the descriptive variables.[9] Hence, each descriptive variable was adjusted for the effects of the remaining three variables. Certain descriptive categories were collapsed due to small cell sizes (fewer than five seropositives)[9,10] or similar seroprevalence rates. For race or ethnicity, white and Hispanic subjects were combined into the referent group white or Hispanic. For region, the Northern Valley, Central Valley, and Southern Valley regions were combined into the referent group California Valleys. The 25- to 29-year and 30- to 34-year age groupings and all persons 35 years of age and older were aggregated. For HIV risk-exposure group, women having sex with someone at risk

TABLE 1.—*Observed HIV-1 Seroprevalence of Women Attending Sexually Transmitted Disease Clinics in 1989 by Demographic and HIV Exposure Characteristics*

Descriptive Characteristic	No. Tested	HIV Positive, No.	HIV-1 Seroprevalence %	(95% CI)*
Race/Ethnicity				
White	5,484	20	0.36	(0.23-0.57)
African American	6,369	64	1.00	(0.78-1.29)
Hispanic	4,469	14	0.31	(0.18-0.54)
Asian/Pacific Islander	496	0	0.00	(0.00-0.73)
Other	231	0	0.00	(0.00-1.56)
Undetermined	161	0	0.00	(0.00-2.22)
Region				
Central Coast	726	4	0.55	(0.18-1.51)
Northern Valley	2,104	8	0.38	(0.18-0.78)
Central Valley	2,823	15	0.53	(0.31-0.90)
Southern Valley	2,750	4	0.15	(0.05-0.40)
San Diego	895	6	0.67	(0.27-1.53)
Los Angeles	3,970	29	0.73	(0.50-1.06)
Bay Area (except San Francisco)	3,433	22	0.64	(0.41-0.99)
San Francisco	509	10	1.97	(1.00-3.70)
Age Group, yr				
≤ 19	3,513	5	0.14	(0.05-0.35)
20-24	4,236	18	0.43	(0.26-0.69)
25-29	3,719	34	0.91	(0.64-1.29)
30-34	2,508	21	0.84	(0.53-1.30)
35-39	1,519	11	0.72	(0.38-1.33)
40-44	797	5	0.63	(0.23-1.55)
45+	833	4	0.48	(0.15-1.31)
Undetermined	85	0	0.00	(0.00-4.14)
Mode of HIV Exposure				
Injection drug use	381	19	4.99	(3.11-7.81)
Blood recipient	163	3	1.84	(0.48-5.71)
Sex with person at risk for HIV	283	3	1.06	(0.28-3.33)
Sex with person of unknown risk	12,046	53	0.44	(0.33-0.58)
Undetermined risk	4,337	20	0.46	(0.29-0.73)

HIV = human immunodeficiency virus

*Confidence interval (CI) was obtained by normal approximation method.

for HIV or someone of unknown risk for HIV, and women who were blood recipients were combined into the referent group "other risk." Where significant deviation between the crude and adjusted odds ratios occurred in each descriptive variable, blockwise logistic analyses[11] were undertaken to determine which variables were responsible for affecting change.

Results

From participating California STD clinics, 17,221 specimens from female clients were included in the survey. Of the 17,210 (99.9%) specimens for which conclusive (positive or negative) HIV-1 results were obtained, 98 specimens were positive, yielding an overall seroprevalence rate of 0.57% (95% confidence interval [CI], 0.46% to 0.70%). Test results for the remaining 11 (0.1%) specimens were indeterminate by Western blot and were subsequently removed from the overall sample.

Prevalence of HIV Infection by Race or Ethnicity, Region, Age, and HIV Risk-Exposure Group

Table 1 shows HIV-1 seroprevalence rates by demographic and risk-exposure characteristics.

Race or ethnicity was obtained for 99.1% of the sample (17,049 specimens). Of the 161 cases where race was not indicated, the HIV-1 seroprevalence rate was 0.00% (CI, 0.00% to 2.22%). Where race or ethnicity was reported, seroprevalence was lowest in Asians or Pacific Islanders (0.00%; CI, 0.00% to 0.73%) and among other races (0.00%; CI, 0.00% to 1.56%), whereas the highest seroprevalence rate was observed among African Americans (1.00%; CI, 0.78% to 1.29%).

TABLE 2.—*Crude and Adjusted* Associations of Women Attending California Sexually Transmitted Disease Clinics in 1989 by Demographic and HIV Exposure Characteristics and HIV-1 Infection*

Descriptive Characteristic	Crude		Adjusted†	
	Odds Ratio	(95% CI)	Odds Ratio	(95% CI)
Race/Ethnicity				
African American	2.97	(1.96-4.51)	3.30	(2.13-5.12)
White/Hispanic‡	1.00		1.00	
Region				
Central Coast	1.55	(0.54-4.45)	2.18	(0.75-6.33)
San Diego	1.95	(0.80-4.73)	2.00	(0.81-4.94)
Los Angeles	2.07	(1.22-3.50)	1.51	(0.88-2.60)
Bay Area (except San Francisco)	1.92	(1.09-3.38)	1.48	(0.82-2.66)
San Francisco	6.08	(2.92-12.63)	3.19	(1.46-6.93)
California Valleys‡	1.00		1.00	
Age Group, yr				
≤19	0.33	(0.12-0.90)	0.36	(0.13-0.96)
20-24‡	1.00		1.00	
25-34	2.09	(1.22-3.56)	1.88	(1.10-3.22)
35+	1.53	(0.81-2.91)	1.59	(0.83-3.03)
Mode of HIV Exposure				
Injection drug use	10.88	(6.42-18.4)	9.34	(5.33-16.4)
Undetermined	1.01	(0.61-1.67)	1.06	(0.61-1.84)
Other risk‡	1.00		1.00	

HIV = human immunodeficiency virus

*Adjusted odds ratios were derived by multiple logistic regression, with the crude risk estimate for 1 descriptive characteristic being adjusted for each of the other 3 descriptive characteristics.

†Multiple logistic regression χ^2 goodness of fit on 109 *df* is 114.94 ($P = .33$).

‡Reference category.

The region of clinic location was obtained for the entire sample. Seroprevalence rates were lowest for women attending clinics in the Southern Valley region (0.15%; CI, 0.05% to 0.40%) and the Northern Valley region (0.38%; CI, 0.18% to 0.78%). Women attending STD clinics in San Francisco (1.97%; CI, 1.00% to 3.70%) and Los Angeles (0.73%; CI, 0.50% to 1.06%) had the highest seroprevalence rates.

Age grouping was obtained for 99.5% of the sample (17,125 specimens). Of the 85 cases for which age was not obtained, the HIV-1 seroprevalence rate was 0.00% (CI, 0.00% to 4.14%). Where age was reported, seroprevalence rates were lowest for women 19 years of age and younger (0.14%; CI, 0.05% to 0.35%) and women 20 to 24 years old (0.43%; CI, 0.26% to 0.69%). The highest seroprevalence rate was noted for women 25 to 29 years old (0.91%; CI, 0.64% to 1.29%).

Information on HIV risk exposure was obtained for 74.8% of the sample (12,873 specimens). Of the 4,337 cases where HIV risk exposure was not indicated, the HIV-1 seroprevalence rate was 0.46% (CI, 0.29% to 0.73%). Where such information was obtained, the seroprevalence rate was lowest for women reporting sexual contact with a person of unknown risk (0.44%; CI, 0.33% to 0.58%). The highest seroprevalence rate was found among women who reported injection drug use (4.99%; CI, 3.11% to 7.81%).

Crude and Adjusted Relative Risk Estimates

Removing categories with zero seropositives did not appreciably alter the observed seroprevalence rates. Overall, 5.6% (959) of cases were omitted. Table 2 shows the crude and adjusted odds ratios (ORs) for study participants by race or ethnicity, region, age group, and HIV risk-exposure group.

Race or ethnicity. African-American women attending STD clinics were three times as likely as white or Hispanic women to be positive for HIV-1 after adjustment was made for other descriptive variables (OR 3.3; CI, 2.1 to 5.1).

Region. Women attending clinics in San Francisco were six times more likely than California Valley women to be positive for HIV-1 (OR 6.1; CI, 2.9 to 12.6). Women attending clinics in Los Angeles, San Diego, and the Bay Area were twice as likely as California Valley women to be HIV-1-positive (OR 2.1, 2.0, and 1.9, respectively). After adjustment was made for other descriptive variables, women attending clinics in San Francisco were still three times more likely than California Valley women to be HIV-1-positive (OR 3.2; CI, 1.5 to 6.9). Women attending clinics in Los Angeles, San Diego, and the Bay Area, however, no longer exhibited elevated risks of infection when compared with California Valley women. Because the odds ratio for women attending clinics in San Francisco was lowered considerably—from 6.1 to 3.2—after adjustment for other descriptive variables, blockwise analyses were evaluated to determine which variables were responsible for this change. Blockwise analyses revealed that adjustment for HIV risk-exposure group was associated with the reduction.

Age group. Women 19 years of age and younger were a third as likely as women 20 to 24 years of age to be positive for HIV-1 (OR 0.3; CI, 0.1 to 0.9). Women 25 to 34 years of age were twice as likely as women 20 to 24 years to be HIV-1-positive (OR 2.1; CI, 1.2 to 3.6). After adjustment, these results were essentially unchanged.

HIV risk-exposure group. Women who reported injection

drug use were almost 11 times as likely as women in the "other risk" category to be positive for HIV-1 (OR 10.9; CI, 6.4 to 18.4). Women with undetermined risk factors were as likely as women of "other risk" to be HIV-1 positive (OR 1.0; CI, 0.6 to 1.7). After adjustment was made for other descriptive variables, women reporting injection drug use had a ninefold increased rate of HIV-1 positivity (OR 9.3; CI, 5.3 to 16.4). Blockwise analyses revealed that adjustment for region was associated with the reduction in the odds ratio (10.9 to 9.3) of women reporting injection drug use.

Discussion

Unlinked serosurveys provide a reliable method of quantifying levels of infection among different populations. The results of these clinic-based surveys are not representative of all sexually active women in California, or even of all California women with sexually transmitted diseases. Differing rates may reflect differences in rates of use of public health clinics by affected groups. Taken in the context of the population served, however, HIV-1 infection rates from these clinics serve as sentinels to underlying rates of HIV transmission.

Women attending STD clinics represent a population group at higher risk for HIV-1 infection than the general population of women in California. The overall HIV-I seroprevalence rate of 0.57% found in this study for women quantifies significant levels of HIV-1 infection. For men attending these same clinics, the overall rate was 3.4% (California Department of Health Services, Office of AIDS, unpublished data, October 1991). The rate for women attending STD clinics was eight times higher than that for women giving birth in the same counties in 1989, with 0.071% of these women HIV-I positive.[12] Among female applicants for military service between October 1985 and March 1991, 0.05% of California women were HIV-1 positive.[13]

Although women who reported injection drug use in this study accounted for only 2% of the overall sample, they accounted for 19% of the HIV-1–positive results. A similar survey in New York City found women who were injection drug users to be 11 times more likely to be HIV-positive than other women presenting to STD clinics.[14] Among women entering drug treatment programs in selected California counties, 4% were HIV-1–positive.[15] The extreme risk of HIV transmission from injection drug use activities cannot be overstated.

Differences in HIV-1 seroprevalence rates among different racial or ethnic groups were significant. After adjustment was made for age, risk factors, and region, rates remained higher among African-American women. Differentially higher rates of HIV-1 infection among African-American women in California have previously been reported. For women giving birth in 1989 in the same counties surveyed in our study, crude rates for African-American women were six times higher than those observed for white and Hispanic women.[12] Race or ethnicity may serve as a marker for an increased risk of HIV infection but does not imply a predisposition for HIV infection. The differences in rates may be partially attributable to risk factors that are not ascertained at the time of clinic visit. Information on HIV risk exposure was obtained by client self-report, and illegal practices such as injection drug use may be incompletely reported in a clinic setting.

Analyses of data for specific regions showed that women attending STD clinics in San Francisco County were most likely to be HIV-1 infected. Differences in rates between most other regions were not significant after adjusting for HIV risk factors, race or ethnicity, and age. Grouping counties into regions, however, may mask significant differences in seroprevalence rates within a single region. For example, the Bay Area region includes the Oakland metropolitan statistical area, which has a crude odds ratio of 2.6 (CI, 1.4 to 4.8) when compared with the California Valleys region. This difference is consistent with the higher HIV-1 rates found among women giving birth in that area.[12] Differences among regions that remain after adjustment may be attributed to overall differences in prevalence of HIV-I among communities in these regions. For example, the prevalence of HIV risk behaviors such as injection drug use may have been equivalent in several areas, but if there were differences in HIV prevalence in these areas, risk behaviors such as needle and syringe sharing in the areas with higher HIV-1 prevalence would be more likely to result in HIV-1 infection.

Results from this study underscore the need for routine HIV counseling and testing services for women presenting with, or being evaluated for, sexually transmitted diseases. Women and their partners should be informed of the associated risk of HIV infection resulting from behaviors such as injection drug use or high-risk sexual activity. Women testing HIV positive should be offered medical and behavioral intervention for HIV disease, including screening for and treatment of gynecologic conditions associated with HIV infection.

Seroprevalence rates for HIV from studies like this one should be used by public health officials to develop region-specific disease control activities. Information on the prevalence of HIV risk factors, as well as rates of HIV infection, can be extremely useful for targeting prevention activities on a local level. Persons involved directly in education and prevention activities should have access to local infection rate data so that these can be actively used and interpreted for community purposes.

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Does Excluding Patients Without Telephones Affect the Results of Telephone Reminder Studies?

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Studies of the effectiveness of telephone reminders to improve the rate of appointments kept have shown conflicting results. Few have accounted for patients without telephones. We conducted a controlled clinical trial to study the effect of excluding patients without telephones in a study of telephone reminders in an urban pediatric clinic. Telephone reminders were attempted the evening before scheduled visits for 238 subjects; 259 controls received no reminders. The overall rate of kept appointments was the same (54%) for both the intervention group and the control group. In neither group was there a substantial difference in the "show" rate between patients with and without telephones (intervention group 52% versus 57%, control group 55% versus 54%). In the intervention group, the show rate was higher for those with telephones who were contacted (66%) than for those who were not (37%) ($P<.001$). Telephone reminders did not improve the overall rate of kept appointments but appeared to result in a significant improvement in the show rate of those who could be reached. Excluding patients who could not be reached by telephone may affect the usefulness of previous studies.

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The numerous studies examining the effectiveness of telephone reminders on the rate of appointments kept in urban clinics serving low-income patients have shown mixed results.[1-10] Some studies reported that telephone reminders had no effect on the clinic rate of appointments kept,[2,4,6,9,10] and others reported improvement.[1,3,5,7,8] Several of these studies excluded patients who had not provided the clinics with telephone numbers[1,5,8,10] or patients who were not reached by telephone.[7] If such patients have a lower "show" rate than that of patients who can be reached by telephone, their exclusion would skew the results toward showing the effectiveness of telephone reminders. Including all patients would lead to a more meaningful conclusion about the effect of telephone reminders on the entire clinic's show rate.

The objectives of this study were to determine whether telephone reminders improved the overall clinic appointment-keeping rate, the rate of appointments kept for patients who had telephone numbers compared with those who did not, and the rate of appointments kept for patients who were contacted compared with those who were not.

Patients and Methods

We conducted a controlled clinical trial at the Harborview Medical Center's Children's Clinic (Seattle, Washington) from April through September of 1989. The clinic serves an ethnically diverse and largely indigent population. About 44% are African American, 33% are white, 15% are Southeast Asian, and 8% are Hispanic, Native American, or other; 70% are covered by Medicaid, and 20% pay out of pocket.

Because this study was undertaken as a quality assurance project, only patients' names and telephone numbers were available for analysis. Other descriptors such as race and payer status were not studied.

Subjects included all scheduled patients on days chosen systematically to represent all parts of the month and each weekday. Controls were all scheduled patients on the next clinic day. We excluded repeat patients—that is, those who had been included in the intervention or control groups and then had another appointment during the study period.

The intervention consisted of a telephone reminder made to each subject who had a telephone number listed with the clinic. Because children almost always come to clinic with a parent or guardian, the term subject refers here to the parent or guardian and child pair.[1]

On the evening before each scheduled appointment, one investigator made all the telephone calls. As many as two attempts were made for each subject. After each reminder attempt, the caller noted whether there had been contact made with the parent or guardian, a message was left with someone else, a communication problem due to little or no English spoken by the person answering the telephone, no answer, a busy signal, an incorrect number provided, or a disconnected telephone. Subjects were counted as reached if contact was made with an adult member of the household telephoned, even if a message was left with someone other than the parent or guardian or if a communication problem was noted.

The results were ascertained from log sheets compiled on each clinic day. Results were classified as "show," cancellation on the appointment day, or "no show." We grouped cancellations on the day of the appointment and no shows together for analysis because late cancellations have the same

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effect as no shows on this clinic's operation. χ^2 Statistical analysis was used to compare groups. Sample-size calculation indicated that 225 subjects per group would give 90% power to detect an improvement from a baseline show rate of 50% to 65%, with a type I error equaling .05.[11]

Results

Of the 497 eligible patients, 238 were in the intervention group and 259 were in the control group. Overall, the show rate was 54% for both intervention and control groups. Telephone numbers were listed with the clinic for 63% (149/238) of the subjects in the intervention group versus 76% (197/259) of controls ($P < .002$). In neither the intervention nor the control group was the show rate substantially different for those who had telephone numbers listed with the clinic versus those who did not (intervention 52% versus 57%, control 55% versus 54%).

In the intervention group, the show rate was greater for those reached by telephone (66%) than for those who were not (37%) (50/76 versus 27/73 [$P < .001$]; Table 1). Of those who were reached, a bigger percentage of the patients with whom direct contact was made kept their appointment (72%, or 42 of 59) than those for whom messages were left (47%, or 8 of 17; $P = .07$). Of 5 patients with whom communication was difficult owing to their poor English comprehension skills, 3 showed. Of the 73 patients who were not reached by telephone, 40 (55%) had disconnected telephones or had wrong numbers listed, 32 (44%) did not answer, and for 7 (1%) the line was busy on both attempts.

TABLE 1.—*Appointment Keeping of Patients With and Without Telephones in a Study of Telephone Reminders*

Patient Group	Patients With Appointments: Kept Appointments, No.	Total	Rate, %
Reminder Group			
With telephones	77	148	52
Reached	50	76	66
Not reached	27	73	37
Without telephones	51	89	57
Overall	128	238	54
Control Group			
With telephones	108	197	55
Without telephones	33	62	54
Overall	141	259	54

Discussion

Telephone reminders did not improve the overall show rate in this urban pediatric clinic population. Although our results confirmed the findings of some previous investigations,[2,4,6,9,10] they differed from others.[1,3,5,7,8,12]

The exclusion of patients without telephones may account for the conflicting results reported in several earlier studies.[1,5] In a previous study at our clinic, telephone reminders did improve the show rate for patients with appointments scheduled more than 14 days in advance.[1] Both telephone and mailed reminders at a neighborhood health center in Pittsburgh substantially improved the show rate compared with controls.[5] In both studies, however, patients without telephones were excluded. In another study, no mention was made of whether or not patients in the study had telephones.[3]

Shepard and Moseley studied the effectiveness of telephone and mailed reminders on the show rates of 1,039 patients at several Boston, Massachusetts, hospital-based outpatient clinics.[8] Those without telephones were assigned to receive a mailed reminder or no reminder. These groups were analyzed separately from those with telephones, who were assigned to receive a mailed reminder, a telephone reminder, or no reminder. Among patients with telephones, the show rate was significantly better for those in the telephone reminder group (62%) than that for the no-reminder group (43%; $P < .001$). Of the patients receiving a telephone reminder, the show rate was significantly better for patients who were reached (86%) than for those who were not reached (51%). If patients with and without telephones were analyzed together, the overall show rate for the clinics would have been improved. About 90% (942) of the patients had telephone numbers, however, so it is not clear whether these results can be applied to a population in which a smaller percentage lists telephone numbers.[8]

Unlike those who found that telephone ownership was associated with an improved show rate,[2,4,8,12] we noted no difference between those who had telephone numbers listed with the clinic and those who did not. Our results indicate that patients who provide telephone numbers to the clinic are no more likely to show for their appointments, especially because so many of the listings are disconnected or are wrong numbers.

We suspect that the patients who are more easily reached by telephone are also more likely to come to clinic appointments, independent of the telephone reminder.[13] As in Shepard and Moseley's study,[8] we found a significant difference in the show rate between the subgroup that could be reached by telephone versus the subgroup that could not be reached, even though subjects for whom messages were left or with whom communication was difficult were included in the reached category. Many of the other telephone reminder studies also reported a higher show rate for patients who were actually contacted.[2,4,5,7-10]

In sum, the use of telephone reminders was associated with a higher show rate for patients with telephones who were reached, but it did not improve the overall show rate in a population in which many patients could not be reached by telephone. Differences in previous studies may be due to the exclusion of patients without telephone numbers listed. Thus, the results of such studies may not be generalizable to groups in which many patients give incorrect or disconnected numbers. When such patients are included, telephone reminders alone do not improve the overall show rate.

The importance of these findings extends beyond the use of telephone reminders to improve the show rate in neighborhood or university-based clinics serving low-income inner-city populations. Any type of reminder, such as mailed or the more recently advocated computer-generated ones,[14] may be less likely to reach indigent patients in the inner city. Clinics instituting any type of reminder system should consider the possible effect of excluding patients who cannot be contacted before concluding that reminders will improve the overall show rate.

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* * *

BIOPSY

(The doctor asks do I want to see?)

I don't know that I do.
A jelly of cells floats
like the medusa, lion's mane.

Tiny blood-weeping tentacles,
a bottle of clues fished up
by a Sherlock Holmes.

Pain has me staring at the ceiling,
bobbing in her adrenaline wake.
The nurse says, call Tuesday,

leaving all weekend for cancer dreams,
a tidepool of proliferation.
I hardly come up for breath,

but swim downstream to a primitive place,
the robed society of my thoughts,
where fear flames like a cross.

I turn cunning as a superstition
to wait out the stone cold cutlery
of the pathologist's eye.

But the news arrives through my body
like a processional,
gradual as light through water,

till it is everywhere, underneath,
another species nosing me up and out
of my own clear, dark womb, reborn.

CHRISTINA ANDERSON McKINLEY©
Mill Valley, California

Conferences and Reviews

Prevention and Treatment of Foot Problems in Diabetes Mellitus

A Comprehensive Program

Discussants

LAURENCE A. GAVIN, MD; RICHARD M. STESS, DPM; *and* JERRY GOLDSTONE, MD; *San Francisco, California*

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith, Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

FLOYD C. RECTOR, MD*: *For patients with diabetes mellitus, a troublesome problem is the development of an infected foot that may lead to the loss of a limb. This is an area of health care in which careful attention to maintenance can make a huge difference. This past year, Laurence Gavin, MD, established a program in our outpatient clinic for the care of diabetic foot problems. For this conference, three specialists in the diabetic foot will discuss this issue. Dr Gavin will outline the magnitude of this problem. There will be subsequent discussions by Richard Stess, DPM, and by Jerry Goldstone, MD.*

Prevalence of Diabetic Foot Problems

LAURENCE A. GAVIN, MD†: We use the term "diabetic foot" to describe the downward spiral of complications that occur in patients with diabetic neuropathy which predisposes them to foot trauma, ulceration, then infection, gangrene, and possibly amputation. In this conference we address the identification of the risk factors that lead to the development of these end-stage foot complications and how to intervene and try to prevent this downward spiral. There is a grim aphorism: "Give diabetes an inch and it will take a foot." A typical case history follows.

Illustrative Case 1

The patient, a 61-year-old man with non-insulin-dependent diabetes mellitus of two years' duration, was admitted to the University of California, San Francisco (UCSF), Medical Center in August 1990 for the management of a right plantar ulcer secondary to burns from a radiator. While in Australia on vacation during the winter, he placed his cold foot on a radiator, fell asleep, and woke up sometime later to the smell of burning flesh. He was transferred from Australia to UCSF for management. His relevant medical history relates to diabetes mellitus that was discovered two years ago in association with an infected left foot and that progressed, resulting in a below-the-knee amputation. Additional complications at that time included proliferative diabetic retinopathy, later treated with laser, and substantial foot neuropathy. He smoked cigarettes. His treatment consisted of diet plus an oral hypoglycemic agent.

Examination at the time of admission showed the retinopathy, left below-the-knee amputation, and an ulcer on the plantar aspect of the right foot. He had normal foot pulses and pressures. We advised more comprehensive care of his diabetes and referral to the High Risk Diabetic Foot Program.

Discussion

Patients with diabetes mellitus are at a much higher risk of gangrene (15-fold) compared with persons without diabetes. Of all our diabetic patients, 20% are admitted to the hospital annually for the care of their feet and associated problems. Half of all nontraumatic major limb amputations are in this patient population. This results in about 35,000 amputations annually in the United States. The amputation rate is 1% overall and 10% for diabetic patients older than 65 years. The dollar cost of this problem is approaching three quarters of a billion dollars per year.[1,2]

Peripheral neuropathy—a diffuse symmetric neuropathy of stocking distribution—is the dominant problem or lesion predisposing to these problems. Pure neuropathy is present in 60% of patients with foot ulcers, pure ischemia in 20%, and combined neuropathy with peripheral vascular disease in the other 20%. Neuropathy with or without peripheral vascular disease is present in as many as 40% of patients with non-insulin-dependent diabetes (type II) after 20 years and is somewhat less prevalent (20%) in those with insulin-dependent diabetes (type I). About 30% of neuropathic patients have insensate feet and are unaware of the neuropathy. After the initial amputation, the problem is progression with future lower extremity amputation in many cases. This occurs in 30% of patients within three years and 50% after five years. Mortality is even more staggering: 50% of patients die within five years after their first major foot or leg amputation. The major causes of death are stroke, heart attack, and complications associated with the diabetic foot.[3-5]

Prevention is the key principle of management. Studies in

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ABBREVIATIONS USED IN TEXT

UCSF = University of California, San Francisco
VA = Veterans Affairs

the United States and Europe have shown that preventing half of these amputations is feasible.[6,7] First we need to recognize and reduce the risk factors associated with this downward spiral of complications. Foot care must be optimized and programs of foot care education established. Studies at established centers for the care of patients with diabetic foot problems have demonstrated the success of integrated, multispecialty care programs. Timely intervention can prevent many of these problems and lead to a dramatic improvement in the quality of life of diabetic patients. This also results in major savings in health care costs.

Defining Risk for Foot Problems

A recent study done by Holewski and others at the Department of Veterans Affairs (VA) Medical Center in San Francisco compared a series of diabetic patients without a history of foot ulceration or amputation with a group of diabetic patients with a history of ulceration or amputation.[8] The aim was to define the risk factors associated with progression. Of 90 patients who were studied, 13 had a history of ulceration and amputation; the rest had no end-stage problems.

Retinopathy was much more prevalent in the group who progressed to amputation or had a history of ulceration. Retinopathy indicates microvascular disease, so it is indirect evidence of microvascular disease in the foot. The group with complications also had abnormal ankle-brachial indexes. This test compares the blood pressure at the ankle with pressure in the brachial artery. A ratio of less than 0.6 indicates serious peripheral vascular disease. Although vasculopathy is an important component, it is not the dominant factor predisposing these patients to foot complications.

Somewhat surprising, bunion deformity and callus formation were not different between the groups. Patients with diabetic foot problems do tend to have an increased incidence of callus associated with abnormal biomechanical pressures, but in this study the difference between the groups was not significant.

The most important differences between the groups related to features associated with neuropathy. Dorsiflexion at the ankle was greatly impaired in the patients with complications as opposed to those without complications. The prevalence of foot deformity, such as hammertoe, showed a dramatic difference. Autonomic neuropathy as determined by EI ratios—the ratio of the mean of the longest RR interval during expiration to the mean of the shortest RR interval during inspiration during deep breathing (6 breaths per minute) and electrocardiographic monitoring—was also significant in those with complications compared with the control group. Finally, peripheral neuropathy as determined by abnormal cutaneous pressure sensations was more prevalent in the group with complications. Ankle reflexes, surprisingly, were not different between the two groups. Thus, this study provides us with a list of significant differences that should indicate high-risk components that predispose to the development of foot trauma, ulceration, and possibly amputation.

It is important to note that these risk factors were present in both groups; it was not an all-or-nothing phenomenon. Despite this possible shortcoming, we have applied these findings as well as risk factors defined in other studies to develop an approach to risk stratification. A weighted risk scale was developed (Table 1) that allows us to stratify patients in low-, medium-, or high-risk groups. The patient in the case presented here would fall into the medium-risk category. He had had previous amputations (weighted value 3), treated retinopathy (1), smoked (1), and had neuropathy (3). These risks add up to a score of 8 on the weighted scale. Vasculopathy is given a low weight on this scale, and, in fact, patients with peripheral vascular disease in the absence of neuropathy, while they are at risk, do not have the high-risk components that we classically see in patients with the neuropathy. The dominant predisposing role of neuropathy and its associated changes such as deformity and gait changes are well documented. Note that patients with Hansen's disease have the same type of peripheral neuropathy as patients with diabetes but have normal circulation; yet, almost identical complications develop. The weighted risk scale has allowed useful comparative studies that have identified the important effects of neuropathy. When used to stratify patients and categorize the levels of risk, this approach facilitates the development of a management plan aimed at the prevention of complications. Thus we can intervene and objectively assess whether or not the intervention is beneficial.

TABLE 1.—*Diabetic Foot Risk Factors for Progression to Ulceration*

Risk Factor	*Weighted Value**
Vasculopathy	1
Structural deformity	2
Loss of protective sensation	3
Heart disease or smoking history	1
No. of years with diabetes (>10)	2
Nephropathy or retinopathy	1
Previous ulceration or amputation	3

*Low risk, 1 to 3; medium risk, 4 to 8; high risk, 9 to 13.

Evaluating Diabetic Neuropathy of the Foot

Neuropathy in diabetic patients is classically of the stocking-and-glove type—peripheral, diffuse, and symmetric. Affected patients have pain, paresthesias, or numbness. Pain, which can be excruciating and a challenge to alleviate, afflicts only a small percentage of diabetic patients who have neuropathy. Most have a history of paresthesia and numbness or, more important, insensate feet. A number of studies, including the VA Medical Center report,[8] emphasize that, in fact, a third of the patients have insensate feet. These patients are typically unaware of this loss of sensation and consequently traumatize their feet, inflict injury, and develop ulcerations, infection, and gangrene that ultimately lead to amputation. The important point is that physicians need to both take a careful history and examine the feet. Careful objective testing must be done to detect and quantify the degree of neuropathy.

Another point is that a diabetic foot with neuropathy is warm, with bounding pulses, and may appear clinically fairly healthy. That foot is at high risk, however. In contrast, a foot with peripheral vascular disease is usually cold, with intact but atrophic shiny skin, absent pulses, and associated with a history of intermittent claudication and night pain.

Although that foot is also at risk, it is not at as high a risk as a neuropathic foot. Thus, the detection of neuropathy should lead to an intense foot-care education program and the development of a comprehensive care plan. A standard examination can detect neuropathy, but does not quantitate the severity. Neuropathy cannot be quantified by pinprick, light touch, or a vibrating tuning fork. It is, however, feasible to quantify neuropathy using Semmes-Weinstein probes. These monofilament nylon fiber probes are attached to a plastic handle. They are carefully engineered and have been used for the past 30 years. They are graded in size so that pressure perception thresholds can be reproducibly determined.[9,10]

The probe is applied to the plantar aspect of the foot. A specific amount of force (pressure) is used to bend the monofilament, and the patient is requested to report sensation. The method used is not just a simple matter of touching; it is called an alternative forced-choice method, and patients are asked whether they did or did not feel the probe. In this way a response bias tends to be obliterated. Testing is performed at six sites on the base of the foot over the metatarsal heads. Requiring detection in at least three of these sites results in a high sensitivity and specificity (>90%).

Using this simple office test, it is feasible to quantify the degree of sensory neuropathy. The sensory perception threshold can be determined, and from this and other associated risk factors, the level of risk for complications can also be determined.

The validity of the data generated by the Semmes-Weinstein probes has been documented by another recent study by Holewski and the San Francisco VA Medical Center group. They studied the following groups: a control group (nondiabetic), a diabetic group without neuropathy, a diabetic group with neuropathy but without complications, and a diabetic group with neuropathy and foot ulceration.[9] Three sites on the plantar aspect of the forefoot were tested to determine the absence of sensation or the degree of sensation reduction. The first two groups (control group without diabetes, and patients with diabetes without neuropathy) had normal sensation. The third group, diabetic patients with neuropathy but without ulceration, had a sensory threshold deficit at the level of 5.07—they could feel this probe size but not smaller probes. The group with ulceration and neuropathy had pronounced impairment of sensation. Their threshold was 6.1, a level indicative of an insensate foot. Using these probes, Holewski and associates were able to differentiate patients without ulcer from those with ulcer in the setting of neuropathy.[9] The 5.07 probe level is now considered to be the sensory protective threshold; patients who have an inability to feel at this probe level are at high risk for progression to foot trauma, ulceration, and gangrene. This study and others have confirmed that the Semmes-Weinstein probes can be used to identify and stratify patients with neuropathy according to the degree of risk.

The development of foot deformity is frequently associated with neuropathy, and this progression places patients in a higher risk category. In diabetic patients with neuropathy, decreased foot fat pads, edematous feet, bunions, callus, hammertoe, and occasionally deformity from Charcot bone-joint degeneration develop. The classic hammertoe deformity in patients with diabetic neuropathy can produce abnormal pressures over the metatarsal heads. These patients have flexion of their toes at the metatarsophalangeal joints and get a cocked-toe deformity. They are at high risk for ulceration on the tops of the toes and, more important, on the ball of the foot. As this deformity develops, the fat-pad protective layer is reduced, the heads of the metatarsals are exposed, and ulceration occurs over the heads. This type of deformity is associated with a notable alteration in the pressure distribution on the sole of the foot and predisposes to these further complications.

After foot abnormalities are detected, I refer patients for further studies to evaluate the extent of foot pressure changes or for vascular analysis. Dr Stess discusses the analysis of foot pressures in the diabetic foot.

Analyzing Foot Pressures

RICHARD M. STESS, DPM*: Our interest in the treatment of diabetic foot problems has evolved and developed over the past five years. Components of the work were originally initiated at the Hansen's Disease Center in Carville, Louisiana. The work of our group at the VA Medical Center in San Francisco was first planned to identify objectively those problems to which Dr Gavin has alluded. We have applied the expertise of Paul Brand, MD, of the Carville center, who noted that repeated high pressure or continuous lower pressures over a period of time will cause localized tissue ischemia. It was not feasible to evaluate the plantar components of foot pressure quantitatively until a new instrument developed in Munich became available in the United States.[11] The VA Medical Center in San Francisco was one of the first centers to obtain the EMED Dynamic Gait System, and there is now one at UCSF.[12] The system involves a sensor platform onto which the patient walks with a normal stride and cadence. The sensor platform is built into a walkway about 6 m (20 ft) long. We attempt to have the patient's foot strike the platform on the third or fourth footstep. The sensor platform, or force plate, contains about 2,000 capacitive transducers, with 2 sensors per cm^2. The maximum force that can be measured is 10,000 newtons, with each sensor achieving a maximum of 127 N. There are several other similar types of pressure analysis instruments available, including the pedobarograph developed by Boulton in England.[13,14] The unique capacitive transducer design of the EMED system, however, allows this unit to produce values that are accurate and reproducible to within 5%. Once the pressures have been obtained, computer analysis allows both a graphic interpretation and statistical analysis of an individual footstep or a grouping of steps. Further, particular zones on the foot can be isolated and then studied for more finite values and a comprehensive evaluation.

Figure 1 shows a computerized summation of pressures (mountain peaks) detected by each sensor throughout the gait cycle. The peaks of pressure visualized can be related to the reference line (87 N per cm^2) to appreciate the relative peaks and troughs of pressure achieved through a normal footstep. A normal gait cycle can be viewed in sequence—heel contact, midstance, and toe-off. The heel-contact phase is illustrated on the right side of the figure. As the footstep progresses to midstance or a flat-foot position, there is a transfer of forces. There is a fairly even distribution of pressure between the heel and the forefoot. As weight is transferred, there is a beginning of higher pressure underneath the second metatarsal. As the heel lifts off the ground, there is a dramatic spiking of pressure (left side of figure) that is far greater than

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the reference line. This is considered the propulsive phase of gait. In a recent study, we determined that most neuropathic diabetic ulcers developed under the ball of the foot during this phase.[13]

In addition to the mountain peak graph, the EMED software allows us to view each footstep in a multihued graph with corresponding graphs for peak pressure, force, and area (Figure 2). Pressures are assigned colors from white (low scale) to magenta (high scale) (here shown as black), which are displayed on the color monitor. Forces greater than 30 N per cm^2 are assigned the magenta color and can be seen easily. The gait line, or the center-of-force line, is the line that the computer calculates and displays on the footprint. The force line visualized in the center graph is biphasic, with the peaks representing heel contact and toe-off. The lower right graph represents the surface area of foot contact with the force plate. The computer allows the identification of specific zones of the foot or times. In essence, to study the function of the foot and determine the normal or abnormal pressure and force patterns, each footstep can be reproduced an indefinite number of times. This is valuable in determining which methods, medical or surgical, might be used in the treatment of a recurrent pathologic foot condition such as a plantar hyperkeratotic lesion or hammertoe deformity.

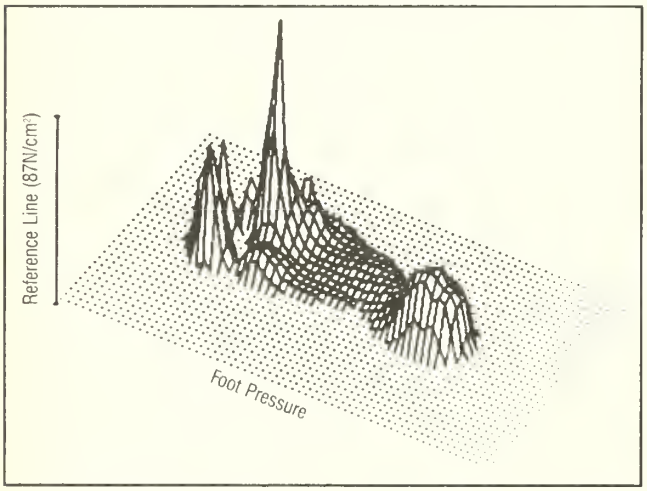

Figure 1.—The summation pressure graph is generated by the EMED Dynamic Gait System during a normal gait cycle. The reference line (left side) represents pressure at 87 newtons (N) per cm^2. The mountain peaks on the sensor grid (2 sensors per cm^2) represent the normal pressure pattern generated (from right to left) by heel contact, midstance, and toe-off during walking.

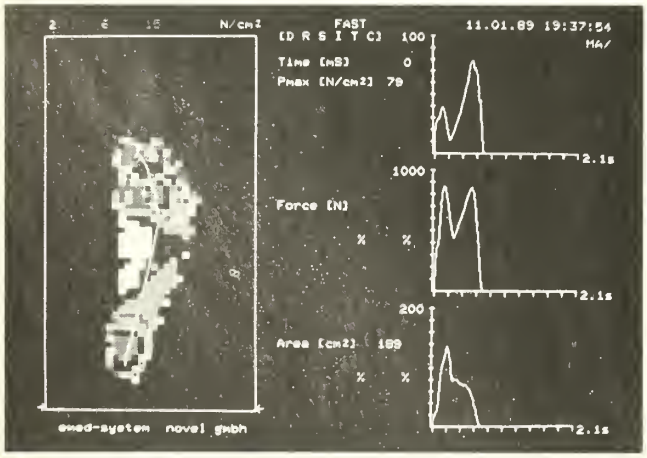

Figure 2.—The EMED measurement shows the pressure distribution during gait as a conformed color picture (left)—given here in black, white, and shades of gray—and as linear graphs (right). The numbers above the picture indicate the various pressure ranges. The linear graphs show the temporal relationship (time horizontal) between pressure (Pmax), force (in newtons), and area (cm^2) at the point of maximum pressure (vertical axis).

Illustrative Case 2

The following case history illustrates the usefulness of the EMED study. The patient, a 68-year-old man with type II diabetes, presented with a Charcot foot deformity. We had been unsuccessful for more than six months in managing a large plantar ulceration despite weekly visits with aggressive debridement of peripheral callous tissue and the provision of custom orthotic devices and molded shoes (Figure 3). An

Figure 3.—A neuropathic midplantar foot ulcer is shown in a 68-year-old man with type II diabetes mellitus and a Charcot foot deformity.

EMED study revealed an abnormally high pressure zone located at the midtarsal joint corresponding to the ulcer site (Figure 4). This pressue continued at this magnitude through the entire gait cycle, indicating that these high pressures were applied to this area of the foot through the entire contact phase of the gait. The pattern, both on the color printout and the mountain peak, differed from the normal pattern shown in Figure 2. An x-ray film of the patient's lateral foot showed substantial deformity throughout the midtarsal region corresponding to the point of persistent ulceration (Figure 5).

Because of the extent of the deformity and continuous pressures over the cuboid, it was thought unlikely that we could successfully manage this patient in a conservative manner. The patient underwent surgical foot reconstruction in which the plantar prominence of the cuboid and the surrounding osseous structures were resected and slightly sau-

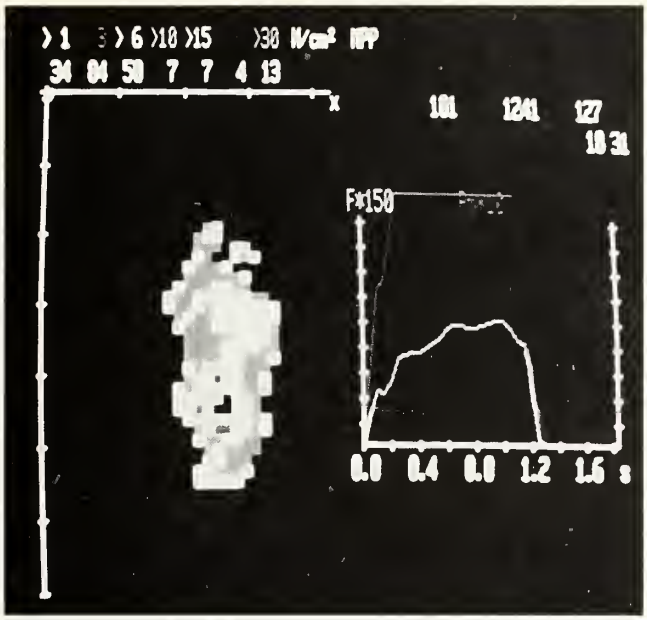

Figure 4.—An EMED study of the foot shown in Figure 3 reveals a high pressure area located to the midtarsal joint (left). The pattern and the graphic pressure printout (right) are grossly abnormal because of the Charcot deformity (compared with the normal pattern in Figure 2). The biphasic pattern is absent, and the peak pressure is 127 N per cm².

Figure 5.—A lateral x-ray film of the Charcot foot deformity shown in Figure 3 reveals substantial deformity in the midtarsal region. The cuboid bone is subluxed and prominent, and the talus is notably plantar depressed and subluxed.

cerized. The postoperative EMED study is shown in Figure 6. The general pattern is not much different from that of the preoperative study, but the peak pressures are now only 61 N per cm² compared with the earlier preoperative study. Although the pattern was the same, the lowered peak pressures resulting from the resection of bone evolved into a lowering of the pressure-time integral. To evaluate the success of the operation, we took individual sensors (Figure 7) similar to those that are built into the force plate and placed them directly on the patient's foot, which was then placed in his shoe. Thus we were able to determine the extent to which pressures were reduced in normal shoe walking.

The EMED system is indispensable in several areas, including in assessing preoperatively and postoperatively corrective foot operations in diabetic patients, in evaluating the effect of insole materials in attenuating peak pressures and forces, and in analyzing the effects of walking and running on the biomechanics of the foot in various types of shoes and barefoot. The EMED system will undoubtedly add to our knowledge and enhance our ability to treat diabetic patients who have neuropathic foot disorders.

Vascular Disease in the Diabetic Foot

JERRY GOLDSTONE, MD*: As pointed out earlier by Dr Gavin, there is a high incidence of lower extremity amputations in diabetic patients, and once a patient with diabetes has undergone a lower extremity amputation, there is a high likelihood of a second amputation being required within three to five years.

Vascular disease is evaluated in functional segments in the lower extremities: aortoiliac, femoropopliteal, and then infrapopliteal or tibioperoneal. One of the characteristics of

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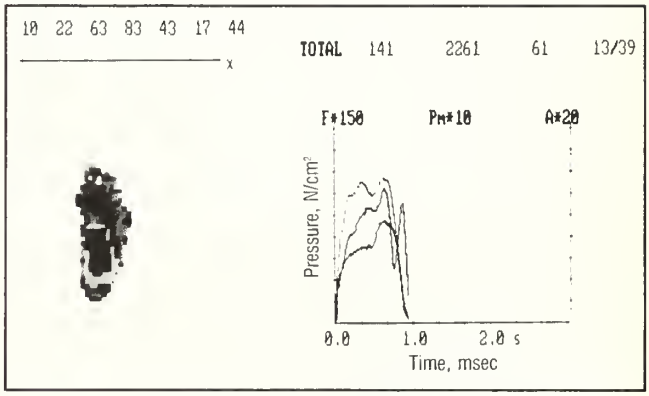

Figure 6.—An EMED study done postoperatively on the Charcot foot deformity (Figures 3 to 5) shows a significant reduction in peak pressure to 61 N per cm², which facilitated healing. F = force, Pm = maximum pressure, A = area

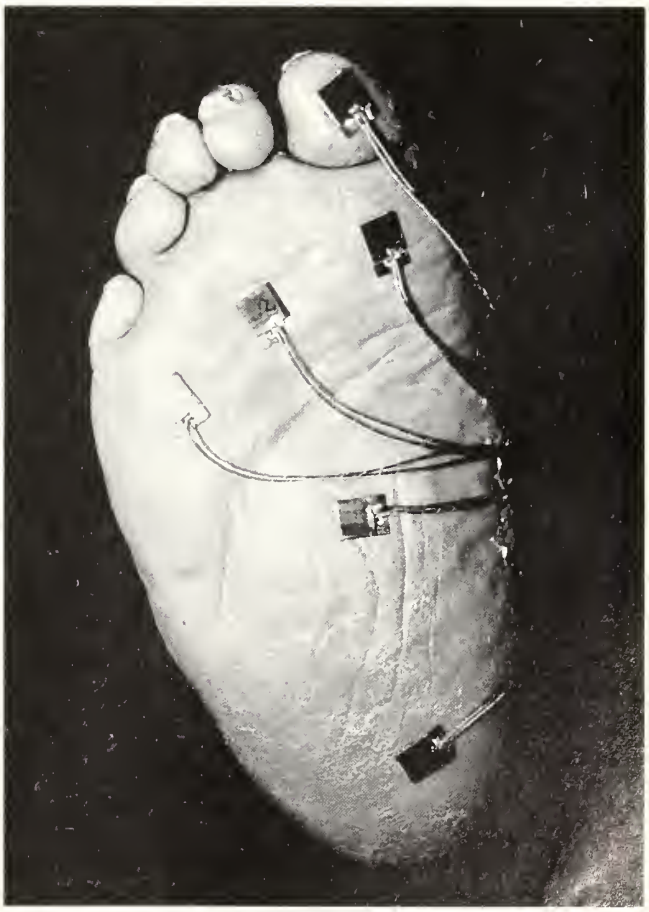

Figure 7.—Individual foot sensors are used to determine foot pressure distribution in the shoe during walking.

diabetic vascular disease is that its distribution is different from that in persons without diabetes. Aortoiliac disease occurs in about 13% of diabetic patients versus 25% of patients without diabetes—that is, diabetic persons tend not to have proximal or aortoiliac disease nearly as frequently as nondiabetic persons do. On the other hand, the profunda femoris (deep femoral) artery tends to be more seriously involved, in both severity and degree, in patients with diabetes than in those without. Lower limb amputations in nondiabetic persons with vascular disease have a typical pattern of superficial femoral artery occlusion with a widely patent deep femoral artery supplying collaterals to the leg. In contrast, diabetic patients typically have widely patent common femoral and superficial femoral arteries but major occlusive lesions involving the profunda femoris artery, with additional lesions further downstream. Disease of the profunda femoris artery is one of the characteristics of diabetes mellitus. The second characteristic is substantial disease below the knee in the tibial arteries, with the relative incidence being about 90% of diabetic persons versus only 10% of those without diabetes. Diabetic patients frequently have involvement of all three of the infrapopliteal arteries. For example, in Figure 8,

Figure 8.—An arteriogram taken below the knee shows the vascular pattern in a diabetic patient. Note the absence of major vessels with collateral formation.

note the lack of any major vessel between the knee and where collaterals begin filling in the midcalf. The recognition of these disease patterns has led to advances in surgical treatment.

Clinical Evaluation of Vascular Disease

The clinical evaluation of the distribution of vascular disease is most important in diabetic patients, and Doppler pressure measurements are of much value. The arteriogram is used only as part of the preoperative evaluation. Diabetic persons also display different patterns of gangrene. Figure 9 shows an infected foot in a diabetic patient. As Dr Gavin indicated, these patients may have normal pulses and normal circulation but are suffering primarily from an infectious process. This is not so much an ischemic problem, at least of the macrovascular type, but is due to neuropathy and microangiopathy, probably complicated by infection. In contrast, patients with focal gangrene of the toes generally have severe macrovascular disease. Figure 10 shows the foot of a patient who had poor foot circulation with absent pulses and occlusion of the major axial arteries.

Figure 9.—Neuropathic ulceration and infection are shown in the foot of a patient with diabetes. There is diffuse involvement due to multiple pressure sites.

Figure 10.—Gangrenous toes occurred in a diabetic patient with extensive macrovascular disease. Ischemic changes are confined to the area of digital vascular distribution.

Clinically, we can obtain some objective evidence regarding the nature of the vascular disease. The simplest approach and the one used most commonly is an evaluation of the ankle-brachial index. This index is the ratio of the systolic blood pressure in the ankle to that in the arm. Normal persons have an index of greater than 1; the blood pressure in the ankle is slightly greater than it is in the arm. Patients who have intermittent claudication tend to have ratios in the range of 0.6 to 0.8. Those who have severe vascular disease, with resting pain or impending gangrene, have levels in the range of 0.1 to 0.3. This gives some quantifiable and reproducible estimate of perfusion of the lower extremities and can be correlated with some of the physical findings.[14,15] In a recent study of patients who had bypass grafts for lower extremity ischemia, the average ankle-brachial index before surgical treatment was only 0.32. This ratio is thus typical for patients with severe disease who often will require distal vascular surgical reconstruction.

Sometimes in a diabetic patient, an "arteriogram" may occur without any contrast medium (Figure 11). Note the outline of the tibioperoneal trunk. The arteries are heavily calcified, and this creates a problem in determining ankle

pressures. The presence of calcification makes the ankle-brachial indexes, or the ankle pressures themselves, unreliable in many diabetic patients. Calcification of vessels leads to an artificially high pressure measurement, and physicians must be careful in evaluating and interpreting the results of simple tests like the ankle-brachial index in diabetic patients.[16] A useful strategy in a diabetic patient who has these "stiff" arteries is to measure toe pressures.[17] Plethysmographic cuffs are available that can be placed around the toes, and an absolute toe pressure can be measured rather than a ratio. When the toe pressure falls below 30 mm of mercury, the likelihood of foot lesions healing goes down dramatically,

Figure 11.—An x-ray film of the leg in a diabetic patient shows advanced arterial calcification.

and, in virtually every category, diabetic patients heal less well than do nondiabetic patients. The ankle-brachial indexes are useful, but if they are normal, it is good practice to measure toe pressures and analyze the waveforms.

Figure 12 shows a diagram of the arterial ultrasonographic waveform. This is a normal femoral artery tracing with a substantial reversed component in diastole. The waveform is a more sensitive index of the degree of arterial insufficiency in a diabetic patient than is the absolute pressure measurement or the ankle-brachial index.[16] Thus, it is possible to detect and quantify vascular disease in diabetic patients with ankle-brachial indexes, with toe pressures, and by examining the ultrasonographic waveforms. These are all simple tests that can be done at the bedside, in a vascular laboratory, and in a diabetic foot clinic.

Vascular surgeons are often asked to see patients who need debridement, amputation, or both. Sympathectomy is seldom used anymore and can be dismissed from consideration in these patients. Arterial reconstruction is often required, with efforts being directed toward salvaging either the foot or, more important, the knee. The techniques that are used are either surgery or less interventional methods. Two new approaches are balloon angioplasty, which seems to work well for local lesions, and laser-assisted angioplasty, which has had tremendous media coverage but unfortunately has not met with much success in patients. In fact, we have abandoned our laser program because it was generally unsuccessful.

Finally, the development of new microvascular instruments, such as intraluminal vein valve cutters and microvascular scissors for cutting valves, has increased the interest in doing bypass operations more distally—that is, onto the foot—than was previously feasible. These instruments have all been developed for use in the so-called in situ saphenous vein technique.[18] For example, it is now possible to extend these bypass operations to the dorsum of the foot using the saphenous vein, and this results in a high rate of limb salvage. Even in diabetic patients the results are good because even among those who have disease at this level, almost every patient has at least one adequate artery in the foot. There are now cases in which it is possible to salvage feet even in a diabetic patient with advanced vascular disease. The keys are an early recognition of the problem and aggressive management of all foot lesions.[19] Through a comprehensive approach, we should be able to save more extremities.

Conclusion

Dr Gavin: I would like to complete this discussion by emphasizing some key points in our approach to the management of the diabetic foot. First, we try to identify patients with high-risk factors for foot trauma. Next, we stratify the patients according to risk and objectively quantify the degree of risk for each individual foot. We must recognize the presence of risks and problems in association with both neuropathy, which is the dominant deficit, and peripheral vascular

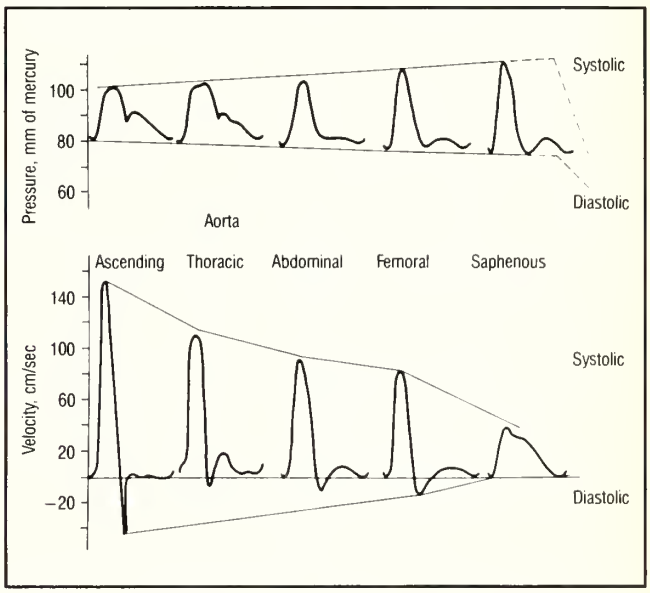

Figure 12.—Doppler ultrasonographic waveform analysis of leg circulation is shown in a normal subject. The normal arterial waveform is triphasic: systolic component (positive), diastolic component (negative), and a low positive rebound. The waveform pattern and amplitude changes are analyzed in the interpretation of ultrasound studies.

disease. Second, once a high-risk state is identified, patients are referred to the appropriate subspecialist, such as a vascular or orthopedic surgeon, for further management. Early intervention for the correction of a foot deformity or timely vascular bypass is critical for foot salvage.

Finally, the interdisciplinary approach is important, as is the availability of a combined care team for the management of diabetic foot problems. One of the first such combined programs was set up at the Joslin Clinic (Harvard University, Boston, Massachusetts), and there are now several excellent centers in the United States and in England. The main reason

for the success of these programs is patient education. All patients must be repeatedly instructed in the dos and don'ts of foot care; handouts are extremely important. A critical aspect of management that is frequently overlooked is that many of these foot problems develop because of poorly fitting shoes. Appropriate shoe prescription and referral to an orthotist for orthotic or custom shoes are important. In addition, patients need close follow-up to determine that the shoes are correct and to reeducate and remotivate them so that they in fact wear the shoes. In the past, these shoes were typically unattractive, and patients refused to wear them. There is no point in having good shoes if patients do not wear them. There now is a fine range of custom shoes available.

Thus, with a well-coordinated foot program, effective intervention is possible. The amputation rate can be reduced by 50%, resulting in a better quality of life for diabetic patients and a considerable saving in health care costs.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *Are all of the diabetics who come to the clinic evaluated with respect to their neuropathy? Are they tested with Semmes-Weinstein probes, and also do they all get an ankle-brachial index analysis?*

DR GAVIN: Yes, all of our diabetic patients are evaluated with the Semmes-Weinstein probes. This is our approach to quantify neuropathy. We also do the other standard clinical tests to check for neuropathy. We subsequently stratify them and place them into the various risk categories. We do an ankle-brachial index in all cases. We have our own Doppler system, so we can measure both the arterial pressures and, as Dr Goldstone pointed out, review the waveform. Depending on the results of those two basic office procedures, we then refer the patient for further studies. If we find abnormal sensation, we refer the patient, especially those with foot deformity, for the EMED pressure study; if the results of the Doppler study are abnormal, we refer to a vascular surgeon for further analysis.

PHYSICIAN IN THE AUDIENCE: *How often do you repeat these tests?*

DR GAVIN: We apply criteria similar to those for the follow-up of retinopathy and nephropathy. We test with the probes on an annual basis for patients at low risk. In a high-risk patient, we check more frequently. Each visit also entails education, the reselection of footwear, foot care, and remotivation. We tell all of our patients, "Wherever you go for health care, always take off your shoes when you enter the doctor's office." Physicians tend not to examine feet. Only 12% of physicians in studies across the country take the time to examine the feet of a diabetic patient. This percentage is considerably higher (80%) in clinics with dedicated diabetes care programs, but even there, foot examination is something that gets overlooked. Patients come in with congestive heart failure and other problems associated with diabetes; these take priority. The feet tend to be neglected.

PHYSICIAN IN THE AUDIENCE: *How is the duration of diabetes weighted as a risk factor?*

DR GAVIN: The duration of diabetes is a risk factor. The patient in the first illustrative case had diabetes diagnosed clinically only two years ago. However, we know that patients with type II diabetes have a long preclinical phase during which complications develop. This patient clearly had advanced diabetic retinopathy and neuropathy. A duration of longer than ten years is considered a risk factor.

PHYSICIAN IN THE AUDIENCE: *It is frequently said that a nondiabetic nonsmoker will not get an amputation for ischemia. My question for Dr Goldstone is, how often do you see ischemic disease requiring amputation in a nonsmoking diabetic?*

DR GOLDSTONE: I really can't answer that definitively, but I think that your impression is correct. We rarely see patients with that degree of ischemia who are not smokers. Almost everybody we see in our practice smokes, and other studies have reported an incidence of smoking of 85% to 90% or higher.

PHYSICIAN IN THE AUDIENCE: *Regarding the EMED system analysis, what does the procedure cost, and how does it add to the whole program that you have described? When should it be ordered? How does it change the management of the diabetic foot or the use of regular podiatric care?*

DR STESS: The EMED is a new instrument. It has only been on the market since 1981 and is currently in operation at only a few medical centers. I think there are about 15 to 20 in the United States that have it, mostly research laboratories. The fee for a comprehensive analysis is $250. The first studies we did were reproducibility studies to make certain that the data were correct and to determine the number of times that we would have to walk a patient on the instrument to get a representative footstep. Each footstep is different, so we walk each patient five times and then derive a mean value to obtain a representative step.

The EMED is influencing our management in a key manner. First, just from a readout we can determine something not previously available—abnormal foot pressure distribution that occurs dynamically. There were previously a great many misconceptions about foot function: where a patient was loading a foot and what the pressure-time integrals were on a particular area. The data that we can now obtain allow us to construct orthotic devices that alleviate high pressure areas. We are also able to determine whether or not a surgical procedure is indicated. Although from an x-ray film bone abnormalities can be seen that result in high pressure, we had no idea before that a footstep takes anywhere from 0.6 to 1.2 seconds. Now we can identify with this instrument the amount of time spent on a particular area of the foot and design treatment, either orthotic devices, custom shoes, or surgery, consistent with the correction of those high pressures and to prevent a breakdown of skin due to pressure trauma.

PHYSICIAN IN THE AUDIENCE: *What is written on a foot prescription for footwear? How much are the charges? Does Medi-Cal or Medicare pay for them?*

DR STESS: There is a demonstration foot project that is being conducted right now by Medicare. If a patient has a history of foot ulceration or if a custom shoe is needed for a patient with diabetes, the project involves submitting a request to Medicare for approval for a custom shoe. Medicare will then randomly assign the patient to a group getting custom shoes or to a control group. Medicare is interested in the therapeutic effect of the shoe and hopes to demonstrate benefits. The cost of a custom shoe in the private sector runs anywhere from $300 to $1,500, depending on the type of deformity. Medicare will pay $300 to $350 for either a custom shoe or what they call an extradepth shoe with a custom insole.

PHYSICIAN IN THE AUDIENCE: *What do you write on the prescription?*

DR STESS: You may request a custom-molded shoe with ac-

commodation or an extradepth shoe with custom insole. Most of the pedorthists (prescription orthopedic shoe makers) have a good idea what is needed. What we do is provide the EMED footprint, isolating a particular area, and request accommodation with certain types of materials.

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Epidemiology of Health and Safety Risks in Agriculture and Related Industries

Practical Applications for Rural Physicians

JAN E. ZEJDA, MD, PhD; HELEN H. McDUFFIE, PhD; JAMES A. DOSMAN, MD; *Saskataan, Saskatchewan, Canada*

Epidemiologic studies document that work in the agricultural sector is associated with many occupational health hazards. Exposure to organic dusts and airborne microorganisms and their toxins may lead to respiratory disorders. The burden of exposure-related chronic bronchitis, asthma, hypersensitivity pneumonitis, organic-dust toxic syndrome, and chronic airflow limitation can be diminished by appropriate preventive measures. The contribution of exposures to agricultural chemicals to cancers and neurodegenerative disorders is being investigated. Some studies document that farmers and those in related industries are at higher risk for the development of cancer of the stomach, soft tissue sarcoma, non-Hodgkin's lymphoma, and multiple myeloma. Chronic encephalopathy and Parkinson's and Alzheimer's diseases are being studied in relation to agricultural chemicals. The possible carcinogenicity and neurotoxicity of pesticides emphasize the need to promote the safe use of chemicals. Another area for health promotion programs is disabling injuries and traumatic deaths. Farm accidents are important because of their frequent occurrence among young people and disturbing fatality rates. Other health issues of concern in these industries include skin diseases, hearing loss, and stress.

(Zejda JE, McDuffie HH, Dosman JA: Epidemiology of health and safety risks in agriculture and related industries—Practical applications for rural physicians. West J Med 1993 Jan; 158:56-63)

Rural physicians have long been aware of illnesses, injury, and premature death among farmers and others in the agricultural industry. A rapidly accumulating body of medical information, however, increases the responsibility of clinicians to be aware of, and to be able to deal with, a variety of serious health and safety risks in the agricultural population.

Over the last decade the issue of health and safety in agriculture has gradually evolved from the existence of sporadic research to a public health priority (Surgeon General's Conference: Agricultural Safety and Health—FarmSafe 2000, A National Coalition for Local Action, Des Moines, Iowa, April 30 to May 3, 1991). Evidence that working in the agricultural sector involves health- and life-threatening circumstances has resulted in the establishment of research centers and in public health initiatives. One is the 1990 Agricultural Initiative, a health surveillance and research program supervised by the National Institute for Occupational Safety and Health (United States Public Health Service).

Health risks in agriculture arise from various exposures, including organic and inorganic airborne dusts and gases, microbes and their toxins, chemicals including fertilizers, insecticides, herbicides, and fungicides, diesel exhaust fumes, physical and mechanical hazards, stress, and behavioral factors. The magnitude of these risks has risen with the increasing industrialization of modern agricultural practices. Two large sectors of agriculture, farming and the grain storage and transporting industry, have been surveyed more comprehensively than other areas. Accordingly, work-related disorders relevant to those occupations will be addressed in the following sections. The major recognized or perceived problems among farming populations include respiratory disorders, cancer, neurologic problems, injuries and traumatic deaths, skin diseases, hearing loss, and stress. The importance of these areas has been documented by several international and national symposia held in the past decade in Canada, Finland, Sweden, and the United States.

Although the scope of this review is limited primarily to epidemiologic issues, it also includes practical points for physicians and other health care professionals. The principal exposures and related medical conditions that we address in this article are summarized in Table 1.

Respiratory Disorders

An excess of respiratory symptoms among farmers has been found in various countries.[1-4] Epidemiologic studies have focused on chronic bronchitis, asthma, hypersensitivity pneumonitis, organic-dust toxic syndrome, and lung function changes. Prevalences of various syndromes are shown in Table 2.[2-14]

Chronic Bronchitis

The prevalence of chronic bronchitis, defined as cough and phlegm lasting for at least two years, ranges from 5.6% to 21.0% (Table 2), almost twice that in nonfarming control subjects[3] and three times higher in nonsmoking farmers than in nonsmoking control subjects.[15] Chronic expectoration is found more frequently in farmers involved in livestock production than in grain farmers[5] and is related to smoking and atopic status.[7] In hog farmers the occurrence of chronic bronchitis is related to the daily duration of work.[16]

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in 1 second
IARC = International Agency for Research on Cancer
Ig = immunoglobulin

Cross-sectional studies conducted in grain workers show that chronic bronchitis may affect 17% to 49% of workers (Table 2). It is associated with the duration of exposure to grain dust [12-14] and is more frequent than in control subjects. Chronic bronchitis also occurs in nonsmoking grain workers.

Asthma

Although the prevalence of asthma in farmers has not been clearly defined, the symptom of wheezing, often considered an epidemiologic marker of asthma, is common (Table 2). In Saskatchewan, the prevalence of wheeze was 27.4% in farmers and 9.9% in control subjects.[3] In Iowa wheezing and shortness of breath were found in 12.8% of retired farmers compared with 3.9% of retired nonfarmers,[1] and wheezing was present in 12% to 30% of swine farmers.[16,17]

Among grain elevator workers, wheezing is found in 24%

TABLE 1.—*Rural Physicians' Primer for Health and Safety in Agriculture*

Organ System or Disorder	*Principal Exposures*	*Possible Medical Manifestations*	*Rural Physicians' Role*
Lungs	Organic dust, microbes, molds, fungi, endotoxins, allergens	Chronic bronchitis, asthma, hypersensitivity pneumonitis, organic-dust toxic syndrome	Recognition, environmental control, appropriate treatment, life-style changes (stop smoking)
Cancer	Herbicides, insecticides, fungicides, fumes, sunlight, diet, unknown	Non-Hodgkin's lymphoma; Hodgkin's disease; multiple myeloma; soft-tissue sarcoma; leukemias; skin cancer; cancer of prostate, stomach, pancreas, testicle; glioma	Early recognition, public health leadership
Neurologic disorders	Herbicides, insecticides, fungicides, solvents, fumigants	Acute intoxication, Parkinson's disease, peripheral neuritis, Alzheimer's disease, acute and chronic encephalopathy	Immediate treatment, diagnosis, public health leadership
Accidents	Tractor rollovers, machine injuries, animal injuries, farmyard injuries	Suffocation, crushing, amputations, eye injuries	Community action, emergency treatment, public health leadership
Hearing loss	Motor noise, animal noise	Deafness	Hearing conservation, diagnosis, treatment
Skin	Pesticides, fuels, fungi, sun, mites, parasites	Dermatitis, dermatophyte infections, cancer	Prevention, diagnosis, treatment
Stress and well-being	Isolation, intergenerational problems, violence, substance abuse, incest	Depression, suicide, poor coping	Accurate diagnosis, counseling skills, community leadership, empowerment

TABLE 2.—*Chronic Respiratory Symptoms in Farmers and Grain Workers—Results of Representative Cross-sectional Studies*

Source	*Occupation and No. of Subjects*		*Chronic Disorders*				*Comments*
			Chronic Bronchitis, %	*Chest Wheeze, %*	*Hypersensitivity Pneumonitis, %*	*Organic-Dust Toxic Syndrome, %*	
Morgan et al, 1975[2]	Farmers	296	11.5-21.0	21.7-26.0	0.12-0.13	--	Hypersensitivity pneumonitis (HP) defined by symptoms (% of clinical diagnoses: 0.02% to 0.05%)
Dosman et al, 1987[3]	Farmers	1,824	11.1*	27.4	--	--	Excess of symptoms in each age category compared with controls
Warren et al, 1987[4]	Farmers	424	--	--	--	15.0	Organic-dust toxic syndrome defined as "flulike symptoms"
Vohlonen et al, 1987[5]	Farmers	7,573	5.6-8.2	--	1.5	--	More bronchitis among livestock farmers; HP defined by symptoms
Malmberg et al, 1988[6]	Farmers	390	--	--	0.4	6.1	HP based on clinical diagnosis; organic-dust toxic syndrome = "febrile reaction"
Iversen et al, 1988[7]	Farmers	1,175	23.6†	16.3†	--	--	Pig farming was a risk factor for bronchitis and asthmatic symptoms
Stanford et al, 1990[8]	Farmers	406	--	--	0.5-15.0	--	Estimation depended on the criteria (less stringent criteria could include organic-dust toxic syndrome)
Marx et al, 1990[9]	Farmers	1,510	--	--	0.4	--	Diagnosis of HP based on extensive clinical evaluation
Chan-Yeung et al, 1980[10]	Grain work	610	34.0‡	32.0‡	--	--	Symptoms related to smoking
Cockroft et al, 1983[11]	Grain work	80	32.5	--	--	16.2	Organic-dust toxic syndrome defined as "flulike episodes"
Cotton et al, 1983[12]	Grain work	390	17.0*‡	28.0*‡	--	--	Symptoms related to smoking and exposure
doPico et al, 1984[13]	Grain work	310	49.0*	42.0	--	32.0	Symptoms related to smoking and exposure
Yach et al, 1985[14]	Grain work	582	35.4*	24.5*	--	--	Symptoms related to exposure and smoking

*Significantly larger than in control group.
†Nonstandard definitions of chronic bronchitis and asthmatic symptoms.
‡Calculated from data in the text.

to 42% of subjects (Table 2).[10,13,14] The prevalence of asthma in these workers, however, is low and likely reflects the selection of susceptible workers out of the industry.[12,18] Symptoms may be allergic or nonallergic in origin as grain dust can induce the direct release of mediators of bronchoconstriction and inflammation, such as histamine, leukotrienes, and interleukin.[19-21]

Grain dust is a complex substance composed of plant debris, insect parts, silica, chemical residues, molds, fungi, and bacteria and their metabolites including endotoxins. Approximately 40% of particles are less than 5 μm in mean aerodynamic diameter and therefore represent a respirable fraction that can penetrate the terminal bronchioles.[22] The complex composition of the dust makes risk assessment difficult, particularly as many constituents of airborne dust in the agricultural environment are recognized as potent allergens.[23,24] In addition, multiple exposures may contribute to dysfunction. For example, we have recently described a possible association between pesticide use and asthma.[25]

Hypersensitivity Pneumonitis

Exposure to antigens from organic dusts may be associated with immunoglobulin (Ig) G and IgA antibody and cell-mediated hypersensitivity, resulting in hypersensitivity pneumonitis (extrinsic allergic alveolitis),[26,27] which is reported to affect 0.1% to 15.0% of farmers (Table 2). Clinically confirmed cases do not appear to be common, however.[9,28,29] Hypersensitivity pneumonitis with its acute or insidious course may present a diagnostic problem—recurrent influenzalike episodes or chronic nonspecific respiratory symptoms—and may lead to chronic respiratory impairment with all the features of pulmonary fibrosis. The principal environmental risk factors for extrinsic allergic alveolitis (farmer's lung) are actinomycetes such as *Micropolyspora faeni*, fungi, and animal proteins present in a variety of agricultural environments.[30,31] The prevalence of hypersensitivity pneumonitis in the grain industry is not known, but because of unfavorable conditions for growth of the offending agents, its occurrence is likely infrequent.

Organic-Dust Toxic Syndrome

The organic-dust toxic syndrome is an acute response to inhaling organic dust, usually characterized by a delayed onset of fever, malaise, and chest tightness[32] without evidence of immunologic involvement and an apparently benign course without persistent respiratory impairment.[23,33] Possible mechanisms include a toxic reaction to endotoxins, mycotoxins, or proteinase enzymes of moldy plant materials.[34] The syndrome may be common, occurring in about 6% to 15% of farmers[4,6] and 10% to 30% of swine growers.[35] The prevalence of acute febrile episodes in grain workers, sometimes called "grain fever," is similar, ranging between 16% and 32% (Table 2).[11,36] Organic-dust toxic syndrome is related to dust level[14] and can be reproduced in subjects experimentally exposed to high concentrations of grain dust.[37]

Lung Function Changes

Acute lung function changes in farmers may be a result of occupational asthma. Some farmers, however, particularly those working in livestock confinement units who do not have clinical asthma, experience across-shift declines in spirometric variables, including forced expiratory volume in one second (FEV_1) and forced vital capacity.[38] These across-shift declines in lung function are associated with increased bronchial responsiveness to inhaled histamine or methacholine. The exact mechanism of acute changes is unclear, but a dose-effect relationship between the inhalation of endotoxins and lung function is possible.[39] In grain workers, in addition to across-shift changes that follow an exposure-response pattern,[40] a decline in the FEV_1 can be observed over the workweek,[41] and a cessation of exposure is associated with an improvement in lung function.[42]

The risk of chronic airflow limitation is likely more common in farmers than in nonfarmers.[3] In swine producers the degree of functional defect relates to the duration of exposure, dust or ammonia concentrations, and endotoxin levels.[16] Data from workers employed in the grain industry indicate an approximately equal effect on long-term airflow limitation of smoking and grain dust.[43] An obstructive respiratory profile is not the only type of impairment found in grain workers, however. The prevalence of a restrictive defect ranges from 7.8% to 9.8%,[8,44] and recent evidence points to the possibility of a restrictive defect as a grain-specific type of respiratory impairment.[45]

The clinical evaluation of agricultural workers possibly having organic dust-related respiratory disorders should include a high index of suspicion. Patients should be interviewed for the relation of symptoms to specific exposures. The occurrence of symptoms during or after certain exposures will assist in the early diagnosis of organic-dust toxic syndrome, asthma, and hypersensitivity pneumonitis.[46] A chest x-ray film, detailed pulmonary function tests, use of the peak flow meter on and off the job, nonspecific and specific bronchial provocation testing, and an immunologic assessment will help to verify the diagnosis and to assess the degree of respiratory impairment.

Rural physicians should be able to provide information concerning exposure hazards, type and availability of respiratory protective equipment, and knowledgeable advice on the appropriate use of devices. For examples of the type of information available, see the Agricultural Respiratory Hazards Education Series, American Lung Association of Iowa, 1986, The Easter Seal Society of Iowa, PO Box 4002, Des Moines, Iowa 50333.

Cancer

The use of herbicides, insecticides, and fungicides in agriculture is now common, and some of these chemicals are known to possess at least low levels of carcinogenic activity in animals.[47] The carcinogenicity of pesticides for humans was reviewed in 1980 by the International Agency for Research on Cancer (IARC) with the following conclusions[48]:

- "The following pesticides and adjuvants are carcinogenic for humans—arsenic and certain arsenic compounds, asbestos, benzene, soots, tars, and mineral oils";
- "The following pesticides are probably carcinogenic for humans—amitrole, carbon tetrachloride, and ethylene oxide";
- "The following pesticides could not be classified as to their carcinogenicity, but require further investigation—chlordane-heptachlor, DDT, dieldrin, and HCH-lindane."

More recently the IARC has concluded that there was sufficient evidence from studies of animals to incriminate dioxin, an impurity in the early production of phenoxyacetic acid herbicides.[49] The experimental evidence suggests that

the possible carcinogenicity of these agents would be through their effect on the immune system. The literature associating pesticide exposure, farming and forestry as occupations, and other farm-related exposures to neoplasms is vast. Table 3 summarizes a selection of articles that confirm these relationships[50-58]; numerous other studies do not.

When all cancer sites are considered, farmers are at significantly lower risk than the population at large.[59] This is especially true of those cancer sites that have been associated with life-style—cigarette smoking and alcohol consumption. As a group, farmers are less likely than people in other occupations to drink alcohol or smoke cigarettes in excessive quantities.[60] The lower prevalence among farmers of cancers of the lung, esophagus, and pancreas has been found in different countries.[61-64]

Farmers and those in related industries appear to be at higher risk for cancers of the stomach and prostate as well as certain rare tumors including soft tissue sarcoma, non-Hodgkin's lymphoma, brain tumors, hematopoietic neoplasms, and cancers of the skin and lip.[50-58] Contradictory results in studies of cancer in farmers may have resulted from imprecision of the definition of exposure, including exposure to pesticides. Many previous studies of cancer and farming used broad categories of exposure such as current occupation (farmer, nonfarmer), pesticide exposure (herbicides, insecticides, biocides), or residence (farm, nonfarm) rather than specific exposures. Many different chemical classes of compounds are used as pesticides, and the type of product used varies with the type of crop grown, weather conditions, farmer preference, and the kind of pest infestation. Additional potentially hazardous exposures that should be evaluated include mycotoxins, fuels, diesel exhaust fumes, gases, lubricants, and organic solvents.

Other factors related to individual exposure include the latency and duration of the use of pesticides, the use of protective clothing, masks, and respirators, and accidents. A study in Saskatchewan showed that fewer than one in three men with occupational exposure to pesticides used protective clothing, one in four used a mask or respirator, one in two had spilled a pesticide on his hands or clothing, and one in two had inhaled a pesticide directly into his lungs.[61]

There are differences in cancer rates for rural versus urban women. The analysis of 1,956 responses to an occupational exposure survey among women with newly diagnosed cancer showed a significantly increased risk for cancer of the corpus uteri among farm dwellers compared with nonfarm dwellers (S. Fincham, Alberta Cancer Board, oral communication, January 1992). As well, significantly low risks for tumors of the cervix uteri, lung, and respiratory tract were found among farm dwellers. McDuffie reported preliminary results of two studies (H. H. M., unpublished data, January 1992). One documented occupational exposure to herbicides (19%), insecticides (29%), grain dust (47%), and diesel exhaust fumes (21%) among rural-dwelling women of middle age. The other, involving a ten-year cancer incidence record review, showed that the rural-to-urban ratio was high for multiple myeloma (1.56; 95% confidence interval [CI] 1.01 to 2.42) and non-Hodgkin's lymphoma (1.53; 95% CI 1.2 to 2.0). Vineis and co-workers have shown an increased risk of soft tissue sarcomas in female but not male rural dwellers exposed to phenoxyherbicides.[65] Donna and associates have shown an association of ovarian tumors with exposure to herbicides.[66] Hoar-Zahm reported an increased risk of multiple myeloma among women who had ever lived on a farm that was equivalent to that of women who had had exposure to insecticides or herbicides (S. Hoar-Zahm, PhD, National Cancer Institute, Bethesda, Md, oral communication, 1991). The sex-related urban:rural ratio invites speculation on the possible role of sex-related differences in the retention of fat-soluble pesticides, but the studies that have attempted to correlate serum and tissue levels of pesticides to disease status or residence in urban or rural areas have produced contradictory results.[67-69]

The contribution of exposure to agricultural chemicals to cancer is difficult to assess. Difficulties ensue with the measurement of exposure, which has to take into account past

TABLE 3.—*Summary of Case-Control Studies Supporting Relationship of Pesticide Exposure and Cancer in Men*

Source	*Cancer Site*	*Exposure and Occupation*	*Odds Ratio*
Hardell and Sandström, 1979[50]	Soft tissue sarcoma	Phenoxyacetic acid	5.3
		Chlorophenols	6.6
Hardell et al, 1981[51]	Hodgkin's and non-Hodgkin's lymphoma	Phenoxyacetic acid	4.8
		Chlorophenols	8.4
		Organic solvents	2.8
Gallagher et al, 1983[52]	Multiple myeloma	Agricultural workers	2.2
Hoar et al, 1986[53]	Non-Hodgkin's lymphoma	Farmers	1.6
		Phenoxyacetic acid	6.0
Woods et al, 1987[54]	Non-Hodgkin's lymphoma	Farmers	1.3
		Herbicide applicators	4.8
		Chlorophenols (>15 years)	1.7
		DDT	1.8
		Organic solvents	1.4
Zahm et al, 1988[55]	Non-Hodgkin's lymphoma	2,4-dichlorophenoxyacetic acid (2,4-D)	1.5
		2,4-D use >20 days/year	3.3
		Chlorinated hydrocarbons	1.4
		Carbamates	1.8
		Organophosphates	1.9
Balarajan and Acheson, 1984[56]	Soft tissue sarcoma	Farmers and gardeners	1.7
Blair et al, 1983[57]	Lung cancer	Pesticide applicators	135*
	Brain cancer		200*
Brownson et al, 1989[58]	Prostate cancer	Farmers	1.3

*Standardized mortality ratio.

exposures and changing agricultural practices. Results of experiments in animals and a number of epidemiologic findings in agricultural populations suggest a link between cancer and pesticides. Rural physicians and public health nurses have important roles as advocates of safe usage practices of chemicals among farmers and users of other chemicals.

Neurologic Disorders

Interest in the neurologic effects of repeated or long-term exposure to agricultural chemicals stems from the toxicologic properties of pesticides, solvents, and other substances commonly used by farmers and from increasing awareness of the sensitivity of the human nervous system to environmental toxins.[70] Two major groups of pesticides, organophosphorus ester insecticides (organophosphates) and contact herbicides (paraquat and its analogues), attract the most attention because of their widespread use and established or presumed biologic activity. Organophosphates and certain carbamates inactivate acetylcholinesterase, an important neuromediator. Paraquat is chemically similar to methylphenyl-tetrahydropyridine, a substance that destroys dopaminergic neurons and causes clinical symptoms of parkinsonism.[71,72]

Other groups of established neurotoxic chemicals, such as the chlorinated hydrocarbon insecticides, mercurial fungicides, and fumigants, may be more of historical interest or they are used by a relatively small group of licensed personnel under controlled circumstances. From an epidemiologic aspect, however, the assessment of past exposures to those chemicals is important in an investigation into the cause of chronic nervous system dysfunction. Current regulations concerning the application of highly toxic chemicals do not eliminate the possibility of secondary exposure. Recognized neurotoxic effects of repeated exposure to hydrocarbon insecticides, carbon disulfide, compounds used as fumigants, or manganese-based fungicides include neurobehavioral dysfunction, peripheral neuropathy, and encephalopathy.[73(p118)-75]

These observations have contributed to the hypothesis that major neurodegenerative disorders may result from an interaction between the host and environmental factors. Exposure to agricultural chemicals has been postulated as a possible risk factor in epidemiologic studies on the occurrence and determinants of Parkinson's disease,[76-87] Alzheimer's disease,[88-90] and chronic encephalopathy.[91-93]

Evidence includes data from a health service register that suggested a correlation between pesticides use and the prevalence of Parkinson's disease in rural areas[76] and the observation that an early onset of Parkinson's disease appears associated with a rural childhood.[77] Case-control studies to investigate relationships between Parkinson's disease and agricultural exposures to organic solvents and pesticides have been inconsistent, however.[78-82] For example, in Sweden, no significant difference in solvent exposure frequency between cases and controls was found for Parkinson's disease,[78] but a marginally increased risk was associated with the previous use of or exposure to herbicides and pesticides in Hong Kong and British Columbia.[79,83] Other studies conducted in China, Kansas, and Quebec found no significant increase in risk associated with exposure to pesticides.[80-82] Recent research conducted in Alberta suggests a herbicide use risk for the occurrence of Parkinson's disease.[84]

In contrast to the toxicologic findings, no specific effects of paraquat or diquat on the human nervous system have been reported in the World Health Organization's report on these chemicals.[85] Nevertheless, further studies on the specific neurotoxicity of agricultural chemicals are warranted by a multifactorial cause of Parkinson's disease, involving rural living among risk factors.[86,87]

Alzheimer's disease is another neurologic disorder of presumed multifactorial origin and increasing public health effects. Although the information about agricultural exposures among risk factors for chronic mental disorders is not available, there are few epidemiologic observations pointing to rural living. Epidemiologic studies addressing regional differences in the prevalence of Alzheimer's disease showed higher rates in mostly rural areas than in other regions of Finland[88] and Italy,[89] possibly as the result of an interaction between aging and the environment in genetically susceptible subjects.[90]

Chronic dysfunction of the central nervous system following acute pesticide poisoning has been documented by case reports and epidemiologic observations.[91,92] Symptoms include headaches, anxiety, fatigue, and disturbed concentration and memory. These symptoms, as well as functional impairment detectable by neuropsychological tests, may reflect the development of chronic encephalopathy as a result of acute intoxication.[93]

A variety of similar nonspecific symptoms of the central nervous system have been reported in studies on the effects of repeated or long-term exposures to organophosphates and fumigants.[94-96] Although the published evidence relates to various occupational groups of agricultural workers, the findings suggest the presence of subtle neurobehavioral changes in subjects with occupational exposure to pesticides. The extent of this problem in agricultural workers and their families, however, remains unknown and is being investigated under the auspices of the World Health Organization and the United Nations.[97]

Investigation into the neurologic effects of long-term exposure to agricultural chemicals is limited by nonspecific and usually subtle symptoms. Except for the symptoms unequivocally related to acute poisoning, describing cause and effect is hampered by unknown exposure-response relationships for nonacute events. Despite the well-known clinical manifestations of acute pesticide poisonings and regulations concerning periodic examination with the measurement of blood cholinesterase activity in workers with regular exposure, case reporting is incomplete.[98] Medical screening by first-contact physicians using a structured interview should facilitate the detection of chronic neurologic sequelae of mild or moderate organophosphate poisonings.

Practicing clinicians should be prepared to recognize both acute and chronic symptoms of exposure and to initiate treatment. This is particularly important in the case of cholinesterase inhibition, where prompt recognition and treatment may be lifesaving.

Injuries and Accidental Deaths

Disabling injuries and accidental deaths represent one of the most disturbing aspects of safety risks in agriculture. Agriculture is the only major industry in the United States that has not shown the marked decline in the number of injuries seen in the mining and construction industries between the years 1962 and 1986. As a result, in 1986 the total number of injuries per 100,000 workers was about 5,400 in agriculture, about 5,200 in mining, and 3,500 in construction.[99]

Agricultural accidents probably claim more lives than do occupational accidents in other industries. In Europe, where about 10 million occupational accidents occur every year (compiled data), mining accounts for 4%, manufacturing for 44%, and agriculture for 9% of all accidents. These industries contribute differently to fatal accidents, however: mining 8%, manufacturing 27%, and agriculture 14%.[100(p47)] In Australia, work-related deaths occur with an estimated annual incidence of 69.8 per 100,000 persons employed in mining, 38.0 per 100,000 in transport, and 22.0 per 100,000 in agriculture.[101]

The annual fatality rate per 100,000 persons engaged in agriculture in the United States, estimated at the level of 52 deaths, exceeds the rate for mining (50 deaths) and construction (35 deaths).[102] The most common cause of death includes tractor-related deaths, followed by those caused by other farm machines—40% to 60% of deaths are related to machinery. Other common causes of death include asphyxiation, falls, felling trees, animal-related, and fire.[99,103]

Reliable data for accidents are difficult to obtain and to compare. The classification of accidents, a reliable estimation of the size of the population at risk, and different statistical methods could be responsible for such differing estimates as 46 deaths and 18 deaths per 100,000 workers, reported for the same year by the National Safety Council and the National Institute for Occupational Health and Safety, respectively.[104]

Farm accidents affect not only farmers themselves but also members of their families. In the United States, in 1981, 73% of all reported farm accidents involved family members, whereas only 22.3% involved hired help.[105] Based on a survey of farm accident victims in Saskatchewan, 44% of accident victims requiring emergency treatment or hospital admission were family members and 34% were farm owners.[106] The highest rates are in young people, with an estimated 23,000 injuries and 300 deaths related to agriculture annually in the United States.[107]

The role of clinicians is twofold: first, rural physicians will be in the frontline for the medical treatment of accidents and should be familiar with current trends in microsurgery and amputated digit-limb reattachment; and, second, rural physicians are in a position to assume a leadership role in prevention.

Skin Problems, Hearing Loss, Stress

Other health and safety risks include skin problems, hearing loss, stress, and mental well-being issues particular to farming and the rural way of life. Skin irritation starts soon after employment commencement and increases to involve more than 60% of workers after four years' employment in the grain industry (P. Pahwa, MSc, Centre for Agricultural Medicine, Saskatoon, Saskatchewan, oral communication, 1991). Skin cancers, dermatophyte infections, and pesticide-related skin diseases are common in farmers. In California, skin conditions account for a high percentage of occupational problems among farmers and other agricultural workers.[108]

Hearing loss is common among farmers. Although little data are available, farmers older than 50 may have as much as 55% hearing impairment,[109] an observation supported by a survey recently conducted in Saskatchewan that showed that a shocking number of farmers, particularly older men, had advanced hearing loss (M. Reesal, MD, Saskatchewan Health, written communication, 1991). Hearing impairment related to noise generated by farm equipment may develop early in life, as suggested by the finding that rural students have a 2½ times greater hearing loss than urban students.[98]

Population-based data are most lacking in the area of stress and psychiatric problems in rural areas. Gross measures such as suicide rates indicate that the number of suicides doubled in Alberta in 1984 compared with 1981, following a serious economic depression—40.6 suicides per 100,000 versus 18.1 per 100,000 in 1981.[110] A similar rate of suicide (48.6 per 100,000) was found in the North-Central states of the United States. This rate was double that for nonfarming white men in the general population.[103] It is likely that these data reflect the tip of the iceberg in an industry that has undergone major economic contraction and social change. Population-based data describing manifestations and intensity of stress among agricultural workers are not available, but there can be little doubt that farming is one of the most stressful occupations in North America.[111]

Summary

Modern agriculture has exacerbated some old and created new risks for the health, safety, and well-being of farm families and others engaged in agriculture and related industries. Farmers, their family members, and others employed in agriculture-related industries should be regarded as an occupational group at risk, particularly for respiratory disorders, cancer, neurologic disorders, injuries, skin problems, hearing loss, and stress. These constitute important areas not only for further research but also for health promotion programs. Epidemiologic evidence, although incomplete, helps to evaluate health risks that are specific to agriculture. Rural physicians should focus on the proper assessment of the agricultural environment in considering etiologic factors. Increased public awareness of the relationships between the environment and health and recent public health initiatives have created an opportunity for comprehensive programs aimed at the assessment of agriculture-related health risks, the initiation of preventive measures, and the evaluation of the effectiveness of such programs.

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Epitomes

Important Advances in Clinical Medicine

Neurosurgery

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in neurosurgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in neurosurgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurosurgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Carotid Endarterectomy

THE FIRST CAROTID ARTERY endarterectomy was done in 1954 on a patient with ipsilateral cerebral transient ischemic attacks. By 1971, 15,000 endarterectomies had been done in the United States, and this number rose to 107,000 in 1985. Although many vascular surgeons and neurosurgeons were convinced of the benefits of this operation, others were skeptical. The 1991 publication of three prospective, randomized, well-designed, and well-executed trials—the North American Symptomatic Endarterectomy Trial (NASCET), the European Carotid Surgery Trial (ECST), and the Veterans Affairs (VA) Symptomatic Carotid Stenosis Trial No. 309—showed unequivocally that surgical intervention is highly beneficial for symptomatic patients with tight carotid stenosis of 70% or more. These remarkable studies have elicited a wealth of new data concerning the natural history of symptomatic carotid artery disease and its treatment with carotid endarterectomy.

The NASCET study showed that carotid endarterectomy reduces the risk of stroke ipsilateral to the stenosis at two years from 26% to 9%, a relative risk reduction of 65% and an absolute risk reduction of 17% compared with the aspirin-only treatment group. The VA study showed an absolute risk reduction of 11.7% in patients with carotid stenosis of greater than 50% and 17.7% in patients with stenosis of 70% or more. The ECST study showed a similar benefit for surgical treatment (85% relative risk reduction). The benefit of surgical treatment in reducing stroke appeared early, within three months, and persisted for at least three years. For major or fatal ipsilateral stroke, surgery provided a relative risk reduction of 81% (13% for medical treatment compared with 2.5% for surgical). Furthermore, the absolute risk reduction for ipsilateral stroke offered by surgical therapy varied directly with the degree of stenosis (26% for 90% to 99%, 18% for 80% to 89%, and 12% for 70% to 79%).

The general conclusion from these studies is that patients with symptomatic carotid stenosis of 70% or greater should be operated on. It is important, however, to consider the inclusion criteria for these trials: transient ischemic attack, minor stroke or nondisabling major stroke of recent onset (less than four months in NASCET, less than six months in ECST), and a life expectancy of five years. The NASCET trial excluded patients with severe intracranial atherosclerotic stenoses, those with major organ failure (kidneys, liver, or lungs), a possible cardioembolic source, or previous ipsilateral carotid endarterectomy.

Because data from several studies have suggested that duplex ultrasound scanning does not always correlate with angiography, a decision regarding surgical intervention should be based on angiography, including the intracranial circulation. The size of internal carotid artery stenosis should be calculated from the luminal diameter at the site of the greatest degree of stenosis compared with the artery diameter beyond the plaque and carotid bulb (NASCET criteria) or with respect to the presumed diameter of the carotid bulb (ECST criteria). The sensitivity and specificity of newer noninvasive imaging techniques—magnetic resonance angiography and rapid spiral computed tomography for carotid artery disease—remain to be determined. If these noninvasive methods prove to be reliable measures of carotid stenosis, they may become extremely useful in the future.

The perioperative major stroke and death rate was only 2.1% in the NASCET study. This reflects the skills that have evolved in surgeons with experience in working with modern equipment and sophisticated anesthesia. Technical improvements, such as intraoperative cerebral monitoring—electroencephalography, somatosensory evoked potentials, cerebral blood flow measurements, and internal carotid stump pressures—as well as the use of intraoperative shunts, magnification, and cerebral protective agents, such as barbiturates and mannitol, have been helpful to various surgical teams, although their use was not shown to decrease or increase the risk of neurologic complications. These adjunctive techniques should be used according to the experience of the surgeon and the circumstances dictated by each case. In patients in whom there is concern about collateral flow during internal carotid clamping (for instance, contralateral carotid occlusion and small posterior communicating arteries, or a change in the intraoperative cerebral monitoring variables), the use of an internal shunt or induced hypertension would be warranted. Obviously hypotension should be avoided during temporary internal carotid artery occlusion.

Whether patients with symptomatic carotid stenosis of 30% to 60% will benefit from endarterectomy is not yet known as the prospective studies have not been completed. At present, such patients should be randomly assigned to one of these trials or a decision regarding surgical therapy made based on the ischemic event, the medical condition of the patient, and the angiographic appearance of the lesion. For instance, the presence of a 60% symptomatic stenosis with an ulcer seen on angiography might weigh more heavily in favor of surgical treatment since the NASCET study showed that ulcers in association with stenosis increased the risk of ipsilateral stroke and that surgery was highly beneficial for such patients. There is no role for surgical intervention in patients with symptomatic stenosis less than 30% because the ECST study showed that endarterectomy actually worsened the results at three years—3.3% ipsilateral stroke in the surgical treatment group compared with 1.3% without an operation.

Two trials—VA Asymptomatic Trial No. 167 and the Asymptomatic Carotid Atherosclerosis Study—are attempting to address another unresolved issue, asymptomatic carotid stenosis. Although it is tempting to generalize the results of the studies on symptomatic patients with high-grade stenosis to asymptomatic patients with similar lesions, this is not yet warranted. The one published study of asymptomatic patients with carotid stenosis of 50% to 90% (Carotid Artery Surgery Asymptomatic Stenosis—Operation Versus Aspirin) showed no benefit of surgical therapy compared with aspirin therapy in these patients. Serious methodologic flaws in the study suggest that the issue remains in doubt, however. Until further data become available, the treatment of patients with asymptomatic carotid stenosis must be carefully tailored to each patient, with a tendency toward conservative management unless the stenosis is severe.

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The Limits of Treatment of Malignant Gliomas

THE DIAGNOSIS OF MALIGNANT GLIOMA—anaplastic astrocytoma and glioblastoma multiforme—has traditionally been associated with a sense of hopelessness for health care professionals as well as patients. Physicians have been taught that the prognosis is uniformly poor regardless of the treatment. This has led to a conservative approach for many patients with malignant glioma, with survival ranging from 12 to 38 weeks.

Recent experimental treatments have failed to extend survival for patients with malignant gliomas. Despite a lack of effective new treatment options, subgroups of patients are "long-term" survivors with standard multimodality therapy. The current clinical challenge is twofold: the selection of patients who are good candidates for multimodality therapy, and the maintenance of quality, not quantity, of life for these patients.

Many factors influence the prognosis of malignant gliomas. Age is probably one of the strongest predictors of survival, as patients aged 18 to 44 years have a median survival of 107 weeks, whereas patients older than 65 have a median survival of 23 weeks. Neurologic function at the time of diagnosis, a history of a previous low-grade tumor, and the histologic composition of the tumor also affect the prognosis substantially. The treatments that influence survival are radiation therapy, surgical therapy, and chemotherapy.

Patients who undergo a complete resection of the tumor, as seen on computed tomography (CT) or magnetic resonance imaging (MRI) scans, have a median survival of 70 weeks, in contrast to a median survival of 19 weeks in patients who undergo only biopsy of the tumor. Magnetic resonance imaging and CT scans do not identify the outermost border of malignant brain tumors; areas that appear "normal" on these imaging studies have been shown to contain tumor cells. Surgical therapy is therefore not curative for high-grade gliomas. An improved ability to identify tumors intraoperatively and map eloquent cortical functions, such as language and motor areas, allows safe surgical resection and cytoreduction in an increasing number of previously "inoperable" patients. Despite no evidence of tumor on postoperative imaging studies, almost all patients have recurrences; 80% of these recurrences will be within 2 cm of the resection margin.

Radiation therapy is still the most effective treatment for these tumors. Regional irradiation in the range of 60 Gy (3 cm beyond the tumor border seen on CT or MRI) is given at most institutions. To preempt recurrences at surgical margins, some centers have recently begun protocols using radioactive seeds (brachytherapy) or stereotactic radiosurgery to boost the tumor margins with single doses as high as 20 to 30 Gy. Most studies using chemotherapy have shown only minimal benefit. Individual patients can respond dramatically to chemotherapy, however, with imaging resolution of the tumor and improved neurologic function. A third of patients will have some response to chemotherapy. In young patients, particularly those with anaplastic astrocytoma, adjuvant chemotherapy with procarbazine hydrochloride, lomustine, and vincristine sulfate has proved beneficial and is extremely well tolerated.

In patients younger than 65 who still enjoy good function, maximum surgical resection, followed by radiation therapy, with a boost to the resection margin, and a trial of adjuvant chemotherapy is currently the most likely approach to maintain quality of life and extend survival. It is essential to observe this group of patients closely with imaging studies repeated every two to three months. Single photon-emission CT scans using thallous chloride Tl 201 are extremely effective in detecting tumor recurrences and in distinguishing recurrence from radiation necrosis. To maintain function and quality of life, it is important to intervene early when tumor recurrence is the likely diagnosis. A second surgical resection or stereotactic radiosurgery can sometimes be effective. Stopping or changing chemotherapy should also be considered. Patients for whom these treatments fail should be considered for experimental approaches, again with the caveat that quality, not quantity, of life should be the goal of treatment.

Strategic planning of an aggressive multimodality treatment approach is best achieved through the collaboration of a "brain tumor team" that includes neurosurgeons, radiation oncologists, medical oncologists, and other health care professionals. This ensures that the patient receives the maximum benefit available from the multidisciplinary treatment of malignant gliomas.

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Indications and Limitations of Stereotactic Radiosurgery

STEREOTACTIC RADIOSURGERY is an important new treatment option for many patients with brain lesions. Although radiosurgical procedures have been used in a limited way for more than 20 years, the development of computerized imaging—computed tomography and magnetic resonance imaging—has created many new applications. By coupling stereotactic localization techniques with a sharply collimated beam, specialized instrumentation makes it possible to target precisely an ablative dose of ionizing radiation to a well-circumscribed brain lesion. With an accuracy approaching 1 mm, a large "necrosing" dose of radiation (10 to 50 Gy) is delivered at one time. Radiosurgical treatment often supplants a craniotomy and is typically done on an outpatient basis. The three basic types of radiosurgical technique are distinguished by radiation source: heavy charged particle; gamma knife, which uses 201 cobalt 60 sources; and linear accelerator-based systems. Radiophysical and clinical studies suggest that under most circumstances the three techniques are comparable.

Radiosurgery has proved to be a valuable tool for treating many benign lesions. For arteriovenous malformations, a single treatment produces intimal hypertrophy and gradual angiographic obliteration over one to two years in 85% to 90% of patients. This result affords permanent protection against rebleeding. During the latent period, however, the risk of rehemorrhage is unaffected. The major complication of radiosurgical treatment of arteriovenous malformations is delayed radionecrosis. The reported risk of this problem ranges from 3% to 9% and is proportional to the volume being irradiated. Smaller but equally effective doses of radiation are currently being used, and the incidence of complications is decreasing. Given the good results that can be achieved with standard neurosurgical resection, radiosurgery is the treatment of choice for small, poorly accessible arteriovenous malformations or patients in poor medical condition.

Radiosurgical ablation is also being used increasingly to treat benign tumors such as acoustic neurinoma and unresectable or recurrent skull base meningioma. By delivering a single large dose of radiation, stereotactic radiosurgery prevents tumor growth in greater than 95% of patients with acoustic neurinomas, and, in 40% of patients, tumor shrinkage occurs. Radiosurgery is associated with transient facial weakness or facial sensory disturbance in 30% of patients. Nevertheless, hearing can sometimes be preserved, especially with smaller lesions. Although radiosurgery prevents symptomatic and radiographic progression in nearly all cases of meningioma, the follow-up of such patients is only a few years. The proximity of the radiation-sensitive optic nerves or chiasm limits the aggressiveness of the radiosurgical treatment of recurrent or unresectable pituitary tumors. New radiosurgical instrumentation and computerized imaging techniques have renewed interest in treating these lesions by these methods. Although radiosurgery has also been used to treat several other types of benign tumors such as hemangioblastoma, craniopharyngioma, and neoplasms of the pineal gland, the benefits of therapy are largely anecdotal. Overall, radiosurgery can be helpful for managing many challenging small benign brain tumors.

Although radiosurgery has been used for only a brief time to treat malignant brain tumors, results have been encouraging. In preliminary studies, a stereotactic "boost" has been used to treat intrinsic malignant gliomas. Furthermore, several investigators have reported impressive local tumor control and minimal morbidity using radiosurgery to treat metastatic brain lesions. Given the relative ease of radiosurgical ablation, this treatment may supplant standard techniques of removing tumors. Clinical trials are in progress to investigate this hypothesis. Ultimately the most widespread use of radiosurgery may be for the management of malignant neoplasms.

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Corpus Callosotomy for Intractable Epilepsy in Children

THE SURGICAL TREATMENT OF medically intractable seizures is now a well-established and expanding aspect of the management of adults with epilepsy. In many cases, the focal epileptogenic area of the brain is first localized by scalp or intracranial electroencephalographic (EEG) recordings and then is excised by craniotomy. The most common operation for seizure in adults is the temporal lobectomy, since partial seizures originating there are relatively common and are frequently difficult to control with anticonvulsants.

Surgical therapy for medically intractable seizures is now being done on patients in the pediatric age range. This is due to several factors. There have been substantial improvements in seizure monitoring and implantable electrode technology. There is mounting evidence to suggest that surgical intervention must occur relatively early in life, before the educational and social deprivation that typically cripples persons with long-standing uncontrolled seizures.

In addition to the relatively rare partial epilepsies, a common epileptic syndrome in children is symptomatic generalized epilepsy. This syndrome may arise as a result of widespread, even bilateral, regions of epileptogenesis and is characterized by a bilateral onset of seizures as recorded by EEG. These attacks occur as atonic "drop attacks," tonic

seizures, and tonic-clonic seizures as well as myoclonic, absence, and akinetic seizures. These epilepsy syndromes do not lend themselves to traditional surgical resection because there is not a restricted epileptogenic focus.

In 1940 the corpus callosotomy was introduced as an operation designed to treat seizures. The theory was that the bihemispheric spread or "synchrony" of the seizure discharge was, in part, dependent on the corpus callosum and the anterior commissure that bound the two hemispheres together. The operation did not receive much attention and was criticized for several reasons: acute severance of the entire corpus callosum produced a profound neuropsychological deficit, a syndrome of "disconnection" consisting of unilateral tactile anomia, left hemialexia, mutism, and unilateral apraxia; and complications of the surgical procedure were high (aseptic meningitis and hydrocephalus were seen after the operation in more than 33% of patients).

In the past decade, most of these problems have been overcome. The neuropsychological deficit is reduced by limiting the sectioning of the corpus callosum to the anterior two thirds. The complications have been mitigated by the use of microsurgical techniques and steroids. The procedure has now become an important tool in the surgical management of generalized seizure disorders, particularly in children. A substantial reduction in seizure frequency has been reported in 78% to 84% of patients undergoing corpus callosotomy for the treatment of generalized and mixed seizures. Although generalized seizures do respond to callosal section, as many as a third of patients with concomitant simple and partial seizures may show an increase in these seizures. Morbidity and mortality have been low. In patients who do not respond to the initial sectioning, there is evidence both for and against proceeding with complete section of the corpus callosum (posterior third).

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Spinal Cord Injuries in Children Without Radiographic Abnormalities

CHILDREN ARE SUSCEPTIBLE to spinal cord injuries without concurrent radiographic evidence of vertebral column disease. In contrast, adult spinal cord injuries are typically accompanied by radiographically detectable fractures or ligamentous spinal injuries. Spinal cord injury without radiographic abnormalities is defined as objective signs and symptoms of myelopathy with normal plain radiographs and computed tomographic (CT) studies. Injuries range from mild transient neurologic symptoms—such as spinal cord concussions—to permanent complete paralysis.

Spinal cord injury without radiographic abnormalities accounts for 30% of spinal injuries in children 8 years of age and younger and for 10% in children between 9 and 16 years old. Young children usually sustain severe neurologic injury; 75% of the injuries in this age group are associated with a complete loss of spinal cord function. Older children (9 to 16 years) usually sustain less severe, typically incomplete neurologic injuries. The cervical or thoracic spinal cord is involved with equal frequency; lumbar injuries are rare.

Although most injuries occur immediately with trauma, children can have a delayed onset of neurologic deficits. Brief, transient motor and sensory symptoms associated with a mild injury are often initially reported. An asymptomatic period can intervene, and after several hours or days, neurologic deficits can develop. Patients who have a delayed occurrence of neurologic deficits tend to have severe or complete neurologic spinal cord syndromes, which may represent spinal cord infarction.

Spinal cord injuries in children should be investigated with thorough radiographic and imaging studies to exclude treatable injuries. The osseous structures should be evaluated by plain radiography and CT. Thin-section CT studies are directed two vertebral levels above and below the clinical level of neurologic injury. Magnetic resonance imaging or myelography is indicated to evaluate for treatable compressive lesions, such as disc herniations or hematoma. Magnetic resonance imaging is preferred because it is noninvasive and precisely delineates spinal cord and soft tissue anatomy and abnormalities.

The pathogenesis of spinal cord injuries without radiographic abnormalities arises from the elasticity and hypermobility of immature spines. The vertebral column in young children is flexible and composed of structurally weak, architecturally immature components. Mechanisms of injury include direct spinal cord traction or compression, an indirect transmission of kinetic energy to the spinal cord, or vascular or ischemic mechanisms. Although rare, treatable causes such as occult fractures, spinal epidural hematomas, disc herniations, occult subluxations, or spinal instability must be considered.

The initial treatment of a patient with documented myelopathy includes maintaining continuous external spinal immobilization and assessing for treatable lesions. A Philadelphia collar or a more rigid brace is used for cervical injuries until neurologic deficits have resolved. Subsequent flexion-extension views of the cervical spine are necessary to rule out latent ligamentous instability. Activity is strictly limited for at least three months because of the risk of recurrent injury. Patients with spinal cord injuries at the thoracic or lumbar level without radiographic abnormalities are initially treated with bed rest and gradual mobilization. Dynamic radiographs are obtained to rule out occult ligamentous instability or late spinal deformity.

A third of children sustain recurrent injuries. Recurrent spinal cord injury without radiographic abnormalities is a serious problem that usually occurs in children with mild initial deficits, the severity of which has been underestimated. These children disregard their immobilization devices and resume normal activities too early. Recurrent injuries tend to result in profound deficits with permanent sequelae.

It has been suggested that children are capable of recovering more function after spinal cord injury than adults with comparable injuries. This notion is based on the unsubstantiated hypothesis that children possess greater plasticity of their central nervous system than adults. The prognosis for these injuries, like the prognosis for all other spinal cord injuries, is related to the severity of the initial injury. Patients with a complete loss of sensory and motor function have a poor prognosis. Children with incomplete neurologic injuries have a better long-term prognosis that depends directly on the severity of the initial motor or sensory deficits. The

objectives of therapy are to provide the maximum potential for neurologic recovery and to prevent recurrent injury. Steroid therapy has not been studied specifically in these patients. Based on the results of treating other patients with myelopathy with methylprednisolone, however, we strongly recommend high-dose intravenous methylprednisolone sodium succinate therapy for patients with spinal cord injury regardless of the cause or radiographic findings. Methylprednisolone should be administered intravenously as a bolus of 30 mg per kg of body weight followed by an infusion at 5.4 mg per kg per hour for 23 hours.

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Management of Growth Hormone-Secreting Pituitary Adenomas—Early Diagnosis Leads to Successful Treatment

ACROMEGALY IS THE LEAST SUBTLE of the hypersecretion syndromes from pituitary adenomas, although it is frequently missed in the early stages of the disease. Not only is the disease disfiguring, it is also disabling and has substantial associated morbidity and mortality. Consequently, the successful management of patients with this disease is dependent on the prompt and proper integration of surgical and medical therapies.

The clinical features of growth hormone (GH) hypersecretion are well known to most clinicians and include coarsening of facial features, enlargement of the hands and feet, and increased water retention within soft tissues. The diagnosis of acromegaly is made by showing elevated basal serum GH and somatomedin C levels along with radiographic confirmation of the presence of a tumor in the sella turcica on magnetic resonance imaging. Occasionally hormonal values will be normal in patients with symptoms suggestive of acromegaly. In these cases, the diagnosis can be confirmed by demonstrating nonsuppression of the serum GH levels during an oral glucose tolerance test. A normal response is a fall in the GH level to below 2 ng per ml after 75 to 100 grams of oral glucose. Similar criteria are used to assess the adequacy of treatment after surgical intervention.

Surgical resection remains the primary mode of treatment of patients with GH-secreting pituitary adenomas. In most cases, a transsphenoidal operation can achieve complete extirpation of the tumor with preservation of normal pituitary function. Only rarely, if the tumor is extraordinarily large, will a craniotomy be required. Resection is contraindicated in severely debilitated patients or when pituitary hyperplasia from a concomitant hypothalamic lesion is suspected. Basal GH levels are expected to return to normal in 60% to 90% of patients after surgical treatment, most frequently when the tumor is a microadenoma (less than 1 cm in diameter) and when the preoperative hormone level is less than 40 ng per ml. In this group, acromegalic symptoms will be relieved and normal pituitary function preserved in greater than 90% of patients.

The medical management of acromegaly is based on the physiologic regulation of GH secretion. An analogue of somatostatin, the natural inhibitor of GH release, has recently been developed that has been shown to cause short- and long-term reduction of GH levels when given in 100-μg subcutaneous injections two or three times a day. In about 50% of people with acromegaly, GH and somatomedin C levels return to normal following octreotide acetate treatment; the associated symptoms and signs are alleviated in 80% of patients. The principal side effect of the medication has been gastrointestinal irritability, and its use has been associated with an increased incidence of gallstones. Although tumor size does decrease in response to octreotide therapy, the effect is not as rapid nor as pronounced as the response of prolactin-secreting macroadenomas to the administration of bromocriptine. The present indications for octreotide therapy include tumors that are not cured by surgical therapy and patients who are not considered surgical candidates. Octreotide may also play a role as a preoperative adjunct to aid the surgical removal of tumor in the future.

Radiation therapy can be considered in patients who do not respond to surgical and medical therapy. Conventional techniques using a total dose of 45 to 50 Gy have been recommended. A hormonal response, however, may take as long as several years and frequently is associated with panhypopituitarism. Stereotactic radiosurgery using the linear accelerator or gamma knife has recently been used to precisely irradiate selected intracranial neoplasms. Several patients with pituitary tumors have been treated, but long-term results are not available at the present time.

The sequelae of acromegaly, including disfigurement, hypertension, cardiomyopathy, and death, underscore the need for the urgent treatment of these patients. In many cases the physical signs and symptoms are reversible. Improved surgical techniques and new medical strategies may allow more effective management in the future.

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Interventional Neuroradiology—A New Approach to Difficult Vascular Lesions of the Brain

INTERVENTIONAL NEURORADIOLOGY has assumed an important role in the treatment of intracranial cerebrovascular lesions, particularly in high-risk patients in whom a poor surgical result would be expected. Such lesions as intracranial aneurysms, vascular malformations, vasospasm following subarachnoid hemorrhage, and thromboembolic stroke are amenable to treatment by the endovascular approach. Either as the sole therapy or in conjunction with a surgical procedure, interventional radiology is proving to be a valu-

able treatment alternative for difficult vascular lesions of the central nervous system.

Highly specific treatment can be administered, including but not limited to the instillation of pharmacologic agents, the injection of particulate embolic substances or glue embolization, the release of detachable microcoils, the inflation of detachable and nondetachable balloons, or a combination of these agents. This less-invasive therapy often allows patients to be discharged from hospital within three days. Some patients require several sessions of therapy, which may be spread out over a period of weeks. Other patients need only a single session. Patients undergoing endovascular therapy are usually selected because they are poor surgical risks or are those in whom conventional neurosurgical techniques are likely to be unsuccessful. As endovascular techniques improve with evolving technology and experience, endovascular therapy will likely become the prime mode of therapy for certain indications.

Intracranial aneurysms can be treated by endovascular occlusion of the aneurysm itself or its feeding artery. This offers the benefits of continuous monitoring of the patient's neurologic status during the procedure, the avoidance of general anesthesia and brain retraction, and immediate high-quality angiography for verification of the procedure's success. For these reasons, several centers have been actively pursuing coil embolization of aneurysms. Small microcoils are pushed through a microcatheter into the aneurysm itself until the aneurysm sac is virtually filled. This may require the placement of multiple coils of varying sizes and configurations. The coils are detached either mechanically or electrolytically. Pitfalls include incomplete thrombosis of the aneurysm, difficulties in access, unintentional aneurysmal rupture or vascular damage, thrombosis of normal adjacent vessels, and ischemic complications. Long-term follow-up for these patients is required. Further research is ongoing, but it is clear that this technique holds great promise.

Intracranial arteriovenous malformations are well suited to endovascular techniques. Surgical access may be difficult or impossible, and some lesions are too large for effective focused radiotherapy. To select patients suitable for treatment, we analyze angiographic risk factors predisposing to bleeding and "steal" symptoms. Endovascular embolization is especially useful as an adjunct to conventional neurosurgical and radiosurgical procedures. Advantages include continuous neurologic monitoring of awake patients, the ability to test vascular territories using intra-arterial administration of amobarbital, and the staged obliteration of the larger malformations to minimize altered hemodynamics. Microcatheters are maneuvered into the feeding arterial pedicles of the arteriovenous malformations, and a rapidly polymerizing cyanoacrylate liquid adhesive is administered to thrombose the arteriovenous malformations. Many pedicles can be devascularized in one session, but the larger malformations require several sessions. A few intracerebral arteriovenous malformations may be cured by this technique, and in most lesions the size of the lesion and blood flow are substantially reduced. Limitations of the procedure are related to vascular access problems, the location of the feeding vessels in critical contiguous areas, and the risks of induced hemorrhage or infarction. In more than 100 such procedures, results have been encouraging, with long-term follow-up continuing.

Symptomatic vasospasm after subarachnoid hemorrhage is still a challenge in neurosurgical management. Endovascular treatments include mechanical dilatation of the vasospastic areas using balloon angioplasty. This technique can be used to reach lesions in large arteries of the circle of Willis. Associated problems include possible aneurysmal rupture if the aneurysm has not already been treated, worsening ischemic changes leading to infarction, and difficulty of access to the narrowest distal arterial branches and perforators, which may be responsible for the ischemic symptoms. The endovascular treatment of vasospasm using pharmacologic agents such as intra-arterial papaverine hydrochloride and other agents may also prove useful. The long-term effects of intracranial angioplasty and pharmacologic treatment of vasospasm are not known and remain a worthwhile avenue of inquiry.

Perhaps the most exciting and rapidly developing indication for endovascular techniques in the cerebral circulation is that of thrombolytic therapy for acute occlusive stroke. While trials of intravenous thrombolytic therapy are taking place at major medical centers, the ability to selectively administer thrombolytic and neuroprotective agents may render our present "treatment" of acute stroke obsolete. Direct intra-arterial administration of urokinase, a thrombolytic agent, into the acutely occluded basilar and carotid vessels has had some success. The results of our limited experience using intra-arterial tissue plasminogen activator to lyse thromboembolic material in the acute stages of stroke appear promising. Far more work needs to be done, but the benefits could be enormous.

Interventional endovascular therapy for cerebrovascular disease has already had important effects. Certain limitations exist, and open microsurgical techniques and stereotactic radiosurgery remain mainstays of treatment in the foreseeable future. Nonetheless, with further technical advances and clinical experience, endovascular therapy for disorders in the central nervous system can be expected to flourish.

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Preventive Aspects of Helmet Safety

HELMET USE HAS BEEN SHOWN to be effective in reducing the extent of injury in both motorcycle and bicycle accidents. Motorcycle helmet use reduces the incidence of severe head injuries by 50%, regardless of the speed limit. After repeal of Kansas's helmet law, the incidence of head injuries increased by 70%, with helmetless motorcyclists at an 81% greater risk of serious injury. In 1990 bicycle helmet use became compulsory in Victoria, British Columbia. It resulted in a marked reduction in the number of hospital admissions of injured cyclists and in the proportion of head injuries compared with the previous year.

In 1974 Congress repealed the US Secretary of Transportation's right to influence states to enforce helmet laws. Ar-

guments to repeal mandatory helmet laws include an infringement on personal rights, the increased rate of accidents due to visibility and hearing limitations (not shown to be true), helmet weight contributing to the severity of injury (not shown to be true), and a lack of proof of effectiveness in preventing injury (not true). Full-coverage helmets have been shown to reduce horizontal peripheral vision by only 3%. Furthermore, a noise loud enough to be heard over the baseline noise of the motorcycle can easily be heard by a helmeted rider.

Research into the construction of helmets has resulted in improved effectiveness and comfort over the cork-lined helmets used during the World War II era. An effective helmet has a plastic or fiberglass rigid shell with a chin strap and an energy-absorbing foam liner. Most impacts to helmets in both motorcycle and bicycle accidents occur on the front and sides with infrequent penetration injuries.

Motorcycle helmet standards are reasonably consistent from country to country. In general the helmet should protect the victims from an impact velocity of 6 to 7 m per second or about 20 to 25 km per hour. These figures are reasonable because 75% of motorcycle injuries occur at less than 48 km per hour. Only in Great Britain is there a standard for faceguard or chin-strap impact testing. The protective properties of the face guard at other than low-velocity impacts remain controversial.

A stiffer shell results in diffusion of the impact and in a rebound of the energy transmission. The protective characteristics of the foam liner depend on the impact velocity. Stiffer foam is more effective at high velocities, whereas a less stiff foam provides more protection at low velocity. Increasing the thickness of the liner leads to a better level of protection at higher velocities but may also increase user discomfort due to the increased mass and weight of the helmet.

Standards for bicycle helmets changed in 1990. The penetration test was replaced by resistance testing to localized loading, thereby allowing the use of soft-shell helmets. In laboratory and field testing, the effectiveness of both the hard-shell and soft-shell helmets was comparable.

Researchers continually strive to construct helmets that offer optimum protection and comfort. The best helmet made is worthless if it sits on the shelf, however.

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Care of Patients With Aneurysms

THE SURVIVAL OF PATIENTS with untreated ruptured cerebral aneurysm is poor. By contrast, surgical treatment is clearly beneficial. It is imperative, however, to make the diagnosis of subarachnoid hemorrhage as soon as possible. The initial bleeding event is often missed. It can be mild, but a subsequent hemorrhage is often devastating if not fatal. Middle-aged patients who present with a severe headache, frequently described as "the worst headache of my life," with or without neck stiffness must be suspected of having subarachnoid hemorrhage, particularly those with hypertension or atherosclerosis. Many patients are misdiagnosed as having flu or other viral illness, migraine (which only rarely starts late in life), or tension headache. Lumbar puncture, computed tomographic (CT) scan, or both will settle the issue in most cases. More severe subarachnoid hemorrhage resulting in mental obtundation with or without neurologic deficit is not usually a diagnostic problem.

The treatment of subarachnoid hemorrhage is surgical in most cases. Traditionally the operation has been done after a waiting period of two weeks to allow the swelling and vasospasm to resolve. The outlook for those patients who improved during that two-week period was excellent. Overall management results, however, indicate that 60% of the patients die or are disabled as a result of rebleeding or vasospasm during that period of waiting. Numerous therapeutic strategies have been developed to manage these complications, including early surgical intervention.

Prospective studies indicate that rebleeding occurs in more than 20% of patients in the first two weeks after the initial bleeding event, with a peak incidence in the first 24 to 48 hours. Mortality associated with a second hemorrhage is high (70% to 80%). Only obliteration of the aneurysmal sac can predictably avert this occurrence. Antifibrinolytic agents, such as aminocaproic acid (Amicar), reduce the incidence of rebleeding but increase the incidence of ischemia and stroke. Induced hypotension has similar deleterious effects. Ischemic deficits from vasospasm develop in a third of patients surviving the initial bleeding event and leave them disabled. While the exact pathophysiology of vasospasm is unclear, the amount of blood in the subarachnoid cisterns predicts the severity of the vasospasm. Induced hypervolemia and hypertension, as well as the use of calcium channel blockers, are now routinely used to combat the effects of vasospasm, but success is only modest. Transcranial Doppler studies and single photon-emission CT scanning can be useful guides to the evolution and severity of vasospasm.

With recent advances in neuroanesthesia, pharmacologic cerebral protection, intraoperative monitoring, and microsurgical instrumentation and techniques, neurosurgeons at a number of centers are turning to early surgical interventions. This is an effort to avert death from spontaneous rebleeding and to protect against rebleeding as a complication of the induced hypertension and hypervolemia used to treat vasospasm. Furthermore, preliminary experience with angioplasty, which can help ameliorate vasospasm in selected patients, indicates that it may be safer following aneurysm obliteration.

Several reports, including the International Cooperative Study on the timing of aneurysm surgery, have documented good results from early surgical intervention. There appears to be an advantage to early surgical treatment in patients who are in good neurologic condition on admission. There are no compelling data on poorer grade patients to recommend early operation, but anecdotal reports suggest that early surgical treatment and aggressive medical management may yield a better result in these patients as well. Other benefits of this treatment include the early removal of intracerebral hematomas, fewer medical complications, probably a lowered incidence of the hydrocephalus that may follow subarachnoid hemorrhage, less psychological stress for the patient and the family, and probably a shorter hospital stay. A somewhat higher operative morbidity and mortality must be accepted

for early surgical treatment compared with traditional delayed operation to realize the benefits in total management morbidity and mortality.

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Epilepsy Surgery for Hippocampal Sclerosis

HIPPOCAMPAL SCLEROSIS is the most frequent pathologic abnormality associated with medically intractable temporal lobe epilepsy. In fact, it is seen in a third of all cases in a random population of patients suffering from epilepsy, as reported both from autopsy cases and in histologic studies on temporal lobes removed during an operation for epilepsy. Hippocampal sclerosis indicates shrinkage and induration of specific regions of the hippocampus with histologic evidence of neuronal loss and secondary astroglial fiber proliferation. There is also a loss of inhibitory hippocampal interneurons and evidence of synaptic reorganization. Hippocampal sclerosis can be either unilateral or bilateral; in some autopsy series, more than half the patients with hippocampal sclerosis had bilateral lesions.

Patients in whom epilepsy manifests itself early seem to show evidence of hippocampal sclerosis more often than patients with late-onset seizures. Bilateral symmetric hippocampal sclerosis is associated with an early onset. The duration of epilepsy, however, does not correlate with the incidence of hippocampal sclerosis. Unilateral, predominantly selective, hippocampal sclerosis is seen in patients with epilepsy beginning later in life. Hippocampal sclerosis can also be seen in infantile spasms and in the Lennox-Gastaut syndrome.

Before any patient with seizures can become a surgical candidate, the patient must undergo a complete evaluation. Patients must be under the care of a neurologist and have seizures that are not controlled with appropriate anticonvulsant therapy. The history and physical examination, scalp interictal and ictal electroencephalograms, magnetic resonance imaging (MRI), and neuropsychological testing are all done to localize the region of epileptogenesis. If the site is localized, an intracarotid sodium amobarbital test should be done to identify the hemispheric distribution of language and memory. If memory cannot be supported by the temporal lobe contralateral to the proposed resection, then the patient is not a candidate for temporal lobe resection.

Magnetic resonance imaging findings help lateralize the seizure focus by showing hippocampal asymmetry. Hippocampal sclerosis may be detected as atrophy of the mesial temporal structures on T1-weighted images and increased signal intensity on T2-weighted images. Other MRI findings, such as atrophy of the adjacent temporal lobe and temporal horn dilatation, may be present. Computed tomographic scanning is rarely helpful because of the relatively poor resolution of the mesial temporal structures. Positron emission tomography may help define regions of functional abnormality, usually hypometabolism, in the suspected temporal lobe.

If the epileptic region is not sufficiently localized to proceed with surgical therapy after the noninvasive evaluation, then intracranial electrodes can be surgically implanted. To define an epileptogenic region thought to be in the limbic cortex, depth electrodes can be implanted in the amygdala and hippocampus through either the inferior or middle temporal gyrus or the occipital lobe. Subdural strip electrodes can also be placed against the inferior and mesial temporal cortex. Recording from lateral temporal or extratemporal neocortex is usually accomplished with subdural strip or grid electrodes placed over the area of interest.

The operation most often done is removal of the temporal lobe en bloc. The procedure should include resection of the amygdala and hippocampus. Depending on the presence of language function in the temporal lobe being removed, as well as the results of the electrical recordings done on the patient, 3.5 to 5.5 cm of lateral temporal lobe measured from the anterior pole is removed. The lateral extent of the resection may be less extensive than the mesial extent.

With this approach, the outcome for these patients is good. After the operation at least 70% of patients are seizure-free with medication or have only auras, 20% have more than 80% reduction in seizure frequency, and 10% have less than 80% reduction in seizure frequency. Most patients who are benefited by surgical treatment will be able to reduce the amount of anticonvulsants that they require, giving them an increased functional capacity. Morbidity from the various surgical procedures associated with epilepsy, such as hematomas or infections, is low, and operative mortality is rare.

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Approaches to Cervical Myeloradiculopathy

CERVICAL MYELORADICULOPATHY is a common cause of radicular pain and weakness in the arms and progressive leg weakness, spasticity, and gait disturbance in the later decades of life. There are two major presenting syndromes of the myelopathy. The first is the transverse syndrome that presents with spastic legs, disturbances of gait, and loss of joint position sense and vibratory sensation in the lower extremities. Individual patients will have varying degrees of severity of the different components. The second syndrome is called the central syndrome and is less common. Involvement is primarily in the upper extremities, where patients will show varying degrees of weakness and sensory loss. There is typically major involvement of the hands with weakness and atrophy of intrinsic hand muscles and sensory loss often associated with dysesthesias. Bladder dysfunction may also be seen. Combinations of the two syndromes are not uncommon.

Degenerative spondylotic myeloradiculopathy is thought

to be the result of chronic, repetitive compressive damage to the cervical spinal cord and roots. Compression may result primarily from anterior spondylotic spurs, posterior infolding of the ligamenta flava, or both. When the myelopathic spinal cord is examined, changes are found that suggest chronic demyelination, vascular compromise, and inflammation of the nerve roots. The exact relationship of this disorder to compressive forces is not fully delineated.

When only one or two levels of anterior spondylotic compression are recognized, anterior cervical discectomy with or without fusion for the removal of the offending osteophytes achieves excellent results. If more than one or two levels of anterior compression are found, then posterior cervical laminectomy has formerly been advocated because of the perceived inability to deal surgically with multilevel anterior disease.

The treatment of cervical spondylotic myeloradiculopathy has changed recently. Surgical approaches are aimed at removing the offending compressive disorder, anterior or posterior, rather than just decompressing the spinal cord so that it can move into a better "position." When multilevel anterior involvement is identified, aggressive anterior approaches, including the partial removal of two or more vertebral bodies, the posterior longitudinal ligament, and any remaining lateral spurs, allows a successful decompression of three or more disc spaces and associated nerve roots. The use of anterior cervical plates has advanced these approaches because the plates serve to anchor and stabilize the grafts and in many cases eliminate the necessity for halo orthosis. The results of aggressive anterior approaches have been excellent, improving on the results of simple posterior decompression alone.

At the same time that aggressive anterior decompression has become more common, simple posterior laminectomy remains an important technique. Laminectomy is indicated for patients with one or two levels of cervical stenosis and root compression, primarily caused by posterior compressive processes, and for those with multilevel disease that cannot be adequately addressed anteriorly. The results of cervical laminectomy compare favorably with those of anterior cervical decompression in these patients.

In the orthopedic literature, there is interest in cervical laminoplasty. This technique, developed in Japan for the treatment of ossification of the posterior longitudinal ligament, seeks to decompress the spinal cord posteriorly and to reconstruct an enlarged cervical spinal canal with intact laminae. By maintaining the integrity of the posterior spinal elements, the potential for postoperative cervical kyphosis and instability is thought to be limited. The results of cervical laminoplasty for cervical spondylotic disease are currently being investigated.

With the introduction of newer anterior and posterior approaches to cervical disorders producing myeloradiculopathies, a careful analysis of cervical compressive pathophysiology is necessary so that appropriate therapy is initiated.

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Metastatic Spinal Tumors

METASTATIC SPINAL TUMORS are common and potentially devastating neurosurgical emergencies. Irreversible paraplegia or quadriplegia may develop rapidly without much warning. Deficits may progress over hours if early symptoms are ignored by the patient or if the diagnosis is delayed. As many as 50% of patients can no longer walk at the time treatment is initiated.

Spinal tumors are metastatic in 89% of cases. The vertebral column is the third most prevalent site of metastatic disease. Spinal metastases are found in 20% to 70% of patients with malignant neoplasms; bronchogenic, breast, prostate, and hematopoietic sources are the most common. Spinal cord compression results in 25% of cases where tumors metastasize to the vertebral column. Neurologic deficit due to vertebral lesions is the presenting symptom in 8% to 14% of cancer patients. The median survival after the onset of spinal cord compression is reported to be as long as 12 to 18 months depending on the tumor cell type, the extent of the primary and metastatic disease, the age of the patient, the severity or rate of progression of the neurologic deficit, and the location or extent of the vertebral neoplasm.

The initial symptom is localized spinal pain and tenderness. Radicular radiation is more common with cervical or lumbar lesions than with thoracic lesions. Spinal pain in a patient with known or suspected malignant disease demands prompt radiographic studies. Numbness and demonstrable sensory deficit beginning two to four dermatomal segments below the site of pain and either preceded or followed by impairment of leg coordination, manual dexterity, or bladder control herald the onset of spinal cord or cauda equina compression. For therapeutic purposes, patients are best classified as asymptomatic, symptomatic but ambulatory, or nonambulatory with complete or incomplete deficits.

Advances in methods for diagnostic magnetic resonance imaging, image-guided needle biopsy, preoperative endovascular embolization for hemostasis, microsurgery for anterior spinal cord decompression, and various instrumentation techniques for spinal stabilization have initiated a quiet revolution in the management of vertebral metastases. Magnetic resonance imaging is the best technique for diagnosing spinal metastases. The entire spinal column can be shown in the sagittal plane, and axial images through the involved segments show epidural mass effect from tumor invasion. The ability to identify the exact extent, site, and cause of spinal cord and nerve root compression or vertebral instability early in the course of metastatic disease has dramatically improved the results of both radiation and surgical therapy.

Mild stable or slowly progressive neurologic deficits caused by radiosensitive tumors are best treated by steroids and radiation therapy. Rapidly progressive but incomplete neurologic deficits require immediate surgical decompression and stabilization if instability exists. Another spinal

complication of metastatic disease that may require surgical attention is pathologic vertebral fracture. Displaced bone fragments in the spinal canal may cause spinal cord compression with or without instability. Subluxation of vertebral bodies, which may cause or aggravate spinal cord compression, may occur when more than 50% of a vertebral body is destroyed, when there is both anterior and posterior vertebral involvement or bilateral posterior involvement, or when there is extensive multilevel disease.

Because as many as 85% of spinal metastases are anterior, the traditional surgical approach of laminectomy offers no better results than radiation therapy (32% to 38% ambulatory after treatment) and is rarely indicated. Anterior cervical, anterior, or posterolateral thoracic and lateral extracavitary thoracolumbar and lumbar approaches for vertebrectomy, radical decompression of the neural elements, and internal fixation relieve pain in 81% to 94% of patients and restore ambulation in 75% of patients with incomplete motor deficits. Vertebral body replacement with acrylic and wire or metallic fixation devices rather than bone grafting is adequate to correct kyphosis and maintain stability for the expected duration of patient survival. Posterior fixation with pedicle screws or rods and sublaminar wires at levels above and below the tumor may also be necessary. With aggressive management of spinal metastases, the quality of survival in patients with malignant disease may be considerably enhanced despite the risks of an operation.

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Alerts, Notices, and Case Reports

Pulmonary Dirofilariasis in California

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Dirofilaria immitis has since the 1960s been considered a parasitic disease primarily of dogs in the southeastern United States. Although veterinarians have been aware of this pathogen and its infection (heartworm) in canine populations, it is becoming apparent that this is an emerging zoonosis capable of substantial human disease. Infections with *D immitis* in humans usually present as pulmonary nodules that are initially suspected to be primary or metastatic carcinoma.

The geographic distribution of human dirofilariasis roughly parallels that of canine dirofilariasis, which has now been reported from all over the United States with the exception of Nevada. To our knowledge only one report of human pulmonary dirofilariasis acquired in California has been published.[1] We report a second case of the disease that was presumably acquired in California. We review its histopathologic features, the prevalence in the canine species in the Redding area of northern California, and the need to consider dirofilariasis in the differential diagnosis of pulmonary nodules in the appropriate setting.

Report of a Case

The patient, a 63-year-old male resident of Redding, California, was admitted January 1991 to Martinez (California) Veterans Affairs Medical Center for evaluation of a right upper lobe nodule. His medical history was noteworthy for transitional cell carcinoma of the urinary bladder treated with partial resection of the bladder and intravesicular chemotherapy in 1987. He said he did not have cough, sputum production, chest pains, dyspnea, weight loss, fever, or a history of or exposure to tuberculosis. In 1988 he experienced unexplained profuse diarrhea for ten months after a partial sigmoid resection for diverticulitis. He has been a resident of the Redding area since 1957 and the owner of two dogs until 1976, when they both died of canine dirofilariasis.

A physical examination elicited no abnormalities. Laboratory evaluation revealed macrocytic anemia with no peripheral eosinophilia. A chest radiograph taken in January 1991 (Figure 1) showed two noncalcified nodules in the right upper lobe, one in the anterior segment and the second in the subpleural space of the right apex. Chest radiographs from 1988 were normal. A computed tomographic scan of the thorax (Figure 2) confirmed the presence of the two nodules, which measured 1.2 cm in the right apex and 1.5 cm in the anterior segment of the right upper lobe. There was no mediastinal involvement. Fiber-optic bronchoscopy did not show an endobronchial lesion, and bronchial washings and cytologic studies were negative for malignant cells. Skin tests were negative for *Mycobacterium tuberculosis*, *Histoplasma capsulatum*, and *Coccidioides immitis*. The results of a fine-needle aspiration were inconclusive. A right thoracotomy and wedge biopsy were done, frozen sections of which revealed portions of a helminth that one of us (J.H.T.) later identified as *D immitis* in the midst of coagulative necrosis. The patient had an uncomplicated postoperative course.

Pathologic Findings

Each wedge contained a single spherical nodule with a necrotic center and a fibrous wall, measuring 1.1 and 1.2 cm in diameter, respectively. On microscopic examination, the center of each was partially caseous and surrounded by a granulomatous zone of palisading histiocytes with Langhans' and foreign body-type giant cells. Transverse sections were taken of two nematodes measuring 125 to 215 μm in diameter that were seen within vessels in one of the granulomas and that appeared necrotic and partially calcified. Each had a thick cuticle with inward longitudinal ridges at the lateral chords. Serial sections revealed recognizable esophageal and genital tube structure, transverse striations on the cuticle, and a coelomyarian muscle. This was subsequently confirmed to be *D immitis* (Figure 3).

Figure 1.—A chest radiograph shows 2 noncalcified nodules in the right upper lobe.

Discussion

Dirofilaria immitis is transmitted only by mosquitoes (vector and intermediate host). Canines, particularly dogs, coyotes, and wolves, are the mammalian hosts, although cases have been reported in cats, foxes, sea lions, bears, and humans. Mosquitoes ingest microfilaria from an infected an-

(Roy BT, Chirurgi VA, Theis JH: Pulmonary dirofilariasis in California. West J Med 1993 Jan; 158:74-76)

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imal during a blood meal, and microfilaria become infectious larvae in about two weeks. As mosquitoes subsequently feed on the hosts, the infective larvae are deposited on the surface of the skin. Eventually they may reach the subcutaneous tissue where they undergo partial maturation for three to four months, migrate through venous channels into the right myocardium, and reach maturity to continue the cycle. In

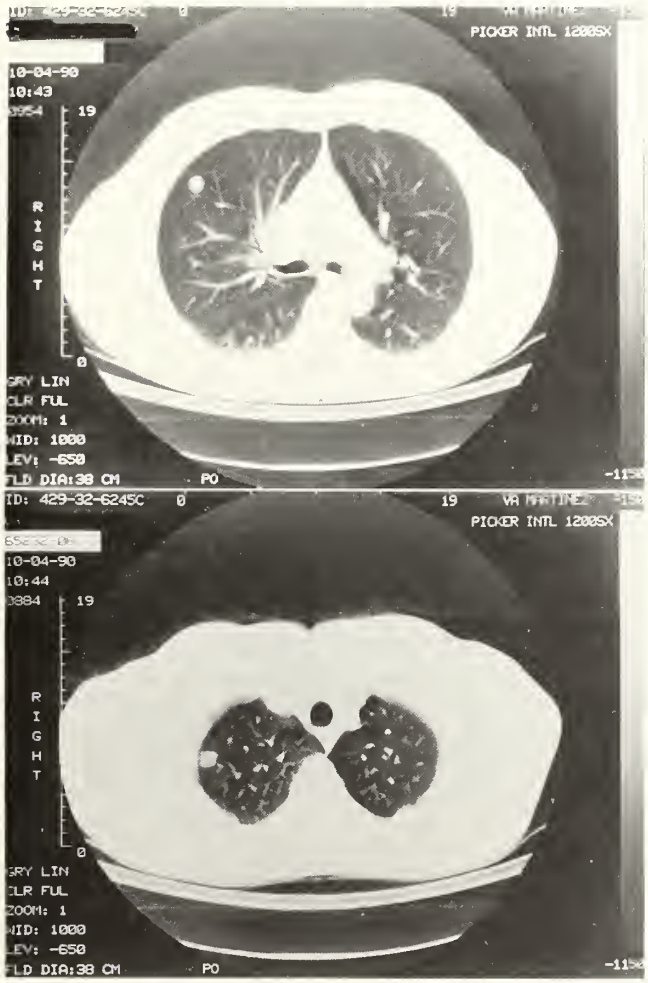

Figure 2.—Computed tomographic scans of the thorax show, **top**, a 1.5-cm nodule in the anterior segment of the right upper lobe and, **bottom**, a 1.2-cm nodule in the right apex of the lung.

humans, maturation to adult worms fails to take place. The worms eventually die and embolize to the pulmonary arteries, producing thrombosis, infarction, and a subsequent granulomatous reaction.

Dashiell in 1961 was credited with the first description of human dirofilariasis involving the lung.[2] Subsequently, more than 60 cases of presumed pulmonary dirofilariasis have been described in the United States.[3] The geographic distribution of human dirofilariasis roughly parallels that of canine dirofilarial infection in this country. Canine dirofilariasis is common in the Atlantic and Gulf Coast states.

In California the distribution of heartworm in dogs and coyotes has been studied extensively.[4-6] More recently data have been collected by one of us (J.H.T., unpublished) on 37,074 dogs from 598 cities in California. The pattern of distribution of heartworm in California dogs is primarily within the foothills of both the Coast and Sierra Nevada mountain ranges. Prevalence rates are directly associated with the 30-year mean annual rainfall of each of 102 cities with 100 or more dogs examined per city and probably correlate with the presence of the mosquito vector. The city in which our patient lived (Redding), has a 30-year mean annual rainfall of 98.8 cm, and in 506 dogs examined for heartworm, the prevalence was 85 per 1,000. This is in contrast to San Jose, which has a 30-year mean annual rainfall of 34.7 cm and a prevalence among 2,975 dogs examined of 3.4 per 1,000, and Bakersfield, with a mean annual rainfall of 15.3 cm and in 251 dogs examined a prevalence of 0. The 11 cities with the highest prevalence of heartworm per 1,000 dogs examined are Sutter Creek, 174; Oroville, 132; Felton, 113; Pine Grove, 107; Grass Valley, 102; Redding, 85; Nevada City, 78; Placerville, 72; Boulder Creek, 52; Lakeport, 52; and Ben Lomond, 47. All of these cities are in the Coastal or Sierra Nevada foothills of California. In contrast to these highly endemic areas, large metropolitan regions such as San Francisco have low prevalence rates (3.7 per 1,000 in 813 dogs examined).

Ciferri describes three major factors that influence the frequency and distribution of human dirofilariasis in a specific geographic area.[1] These include the size of the canine population, the prevalence of canine dirofilariasis in that population, and the density of the vector mosquito population. All of these factors now exist in northern California, making human pulmonary dirofilariasis likely to occur. The other reported case of pulmonary dirofilariasis was in Placer County, also in northern California.

A review of the literature shows that human dirofilariasis occurs predominantly in whites (94.7%), in their fifth or sixth decades of life, with a male-to-female ratio of 2:1.[7] Symptoms, commonly chest pain, cough, or hemoptysis, were present in 37.6% of patients. Most patients (62.4%)

Figure 3.—A transverse section of partially calcified nematodes shows recognizable esophageal and genital tube structure of canine heartworm *(Dirofilaria immitis)* (original magnification × 250).

were asymptomatic, and the disease was discovered incidentally on routine radiography or during investigation of another problem. The radiographic findings consisted of a single (89.8%) or multiple (10.2%) pulmonary nodules that simulated primary or metastatic lung tumor.[8] Pulmonary nodules with pleural effusions have also been described.[9] Tests for peripheral eosinophilia, serologic tests, bronchoscopy, and needle aspiration are frequently nondiagnostic.

Unfortunately, difficulty exists in differentiating pulmo-

nary dirofilariasis from lung cancer. Although serologic tests are available—enzyme-linked immunosorbent assay, indirect hemagglutination—they lack specificity. In addition, cross-reactivity with other helminths is common, further reducing the value of these tests. Although one case was diagnosed by fine-needle aspiration,[10] thoracotomy with wedge resection and histopathologic examination is the most reliable method of making a definitive diagnosis.

Conclusion

We report a second case of human dirofilariasis in a California city that has a high prevalence of canine dirofilariasis. More cases of pulmonary dirofilariasis in humans are likely to be found with a greater awareness of this condition. Clinicians, especially those in northern California, should include this disorder in the differential diagnosis of a case of unexplained single or multiple pulmonary nodules.

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Editorials

Sentinel Surveillance and Prevention of HIV in Women

As of July 1, 1992, there were 43,402 adults with the acquired immunodeficiency syndrome (AIDS) reported to the California Department of Health Services, and 30,226 deaths.[1] Of all adults with AIDS, 96% were male and 4% were female. Surveillance data on AIDS, although of great importance, may not totally reflect the current status of the human immunodeficiency virus (HIV) epidemic in a community. In some adults, the time from HIV infection to the development of AIDS may be ten years or longer[2]; therefore, emerging trends in HIV infection may not yet be reflected in diagnosed cases of AIDS. Also, some persons with HIV infection may have signs and symptoms of illness not included in the current surveillance case definition for AIDS.

For these reasons, many surveillance programs have included studies to evaluate the prevalence of HIV infection.[3,4] One approach to HIV surveillance is to conduct surveys of a random sample of the general population. Although this may give information about the rate of infection in that population, such studies require extensive resources and planning. Another approach is to conduct systematic surveys in selected groups of special interest. Some of these sentinel populations may represent persons at increased risk for HIV infection, such as those attending clinics for the treatment of sexually transmitted diseases (STDs) or injection drug users in methadone maintenance programs. Although these groups may not be representative of the general population, data from such surveys can provide valuable information about the HIV epidemic in a community. Because such groups may also be targeted by AIDS prevention programs, sentinel seroprevalence data may be important for planning and assessing intervention activities.

In this issue, Wilson and colleagues report findings from HIV seroprevalence testing among women attending STD clinics in California.[5] Unlinked surveys were conducted during 1989 at clinics in 21 of California's 61 local health jurisdictions; most clinics were in urban settings. The overall HIV seroprevalence rate was 0.57%, with a higher rate (1.00%) among African-American women. As the authors indicate, these data cannot be generalized to indicate the rate of HIV infection among other women in California; for example, blinded serosurveys of blood specimens taken from newborns indicate a lower rate of infection among childbearing women in California.[6] Even among women attending STD clinics, there was regional variation in HIV seroprevalence; therefore, women attending STD clinics in other health jurisdictions that were not included in this study may have had a different prevalence of infection. The prevalence of infection for a specific health jurisdiction may have also depended on the population attending the specific clinics where sampling was conducted.

Nonetheless, the women tested in this sentinel survey represent an important group at risk for AIDS. Heterosexual transmission is a major source of HIV infection among women throughout the world.[7] Among women with AIDS in California, 33% are reported to have been infected through heterosexual contact.[1] The number of women actually infected through heterosexual transmission may be larger and could include some women who also report injection drug use (and are therefore placed in this risk category). Still other women may have also become infected through sexual intercourse with a male partner; however, because this partner was not known to be HIV infected or at risk for HIV infection, these women may have been placed in the risk category of "None of the above or other."[8]

Evaluating persons attending STD clinics is also important because the presence of other STDs may facilitate the likelihood of HIV transmission. Several studies have implicated genital ulcer disease as a risk factor for the sexual transmission of HIV.[9] Nonulcerative STDs (such as chlamydia and gonorrhea) were also associated with an increased risk of HIV infection in a study of female prostitutes in Africa.[10] Therefore, among all women, those presenting with STDs may be particularly at risk for HIV.

Wilson and colleagues also report that women with a history of injection drug use had a higher prevalence of HIV infection, with an adjusted odds ratio of 9.34.[5] Injection drug use has an important impact on the HIV epidemic among women in several ways. Among women with AIDS in the United States, 50% report a history of injection drug use.[11] An additional 21% of women with AIDS reported heterosexual contact with an injection drug user. Therefore, injection drug use may directly or indirectly account for a substantial proportion of HIV infection among women in this country.

An essential component of epidemiologic surveillance is the use of this information for planning, implementing, and evaluating public health interventions.[12] Wilson and associates make the important recommendation that HIV seroprevalence rates from these studies be used to develop region-specific disease control activities.[5] A priority for such control programs is reducing the sexual transmission of HIV. To help achieve this goal, prevention activities may include the promotion of barrier contraceptives and training to help women successfully discuss and negotiate sexual practices with their partners. Women attending STD clinics represent an important group to target for such education. A second priority for control programs is reducing HIV transmission among injection drug users. Achieving this goal requires continued support for and objective evaluation of a variety of potentially effective intervention activities, including drug treatment and needle exchange programs.

Nationally, the proportion of AIDS cases among women has been increasing over time.[13] Infection with HIV or AIDS is emerging as one of the leading causes of death among US women 15 to 44 years of age.[14] In addition, some HIV-infected women will give birth to HIV-infected infants. Despite budget cutbacks and other resource limitations, it is critical that government agencies continue to work with health care professionals and community and private organizations to help prevent AIDS in all women and men at risk for HIV infection.

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An Optimistic Message for Foot Problems in Diabetes

TEN YEARS AFTER the discovery of insulin, Joslin reported that diabetic gangrene was a menace to his patients.[1] Even today, foot problems remain one of the commonest reasons for hospital admission among patients with diabetes mellitus despite the major advances that have been made in prevention and treatment during the last decade.

Neuropathy and peripheral vascular disease are the two most important factors associated with foot problems. Other factors that have been implicated are limited joint mobility and reduced resistance to infection due to impaired leukocyte function.

Motor neuropathy in a diabetic foot leads to small muscle atrophy and a consequent imbalance between flexor and extensor muscles, which ultimately results in clawing of the toes, prominent metatarsal heads, moving of the footpad forward, and the development of high foot pressures under the metatarsal heads during both walking and standing. High pressures combined with dry brittle skin, a result of the autonomic neuropathy, lead to callus formation that acts as a foreign body, further increasing the already high pressures that are applied at the healthy tissues.[2] This chronic and repetitive moderate stress can lead initially to an inflammatory reaction and, if the foot is not rested, to ulceration. The role of sensory neuropathy at this point is crucial: the pain unawareness allows the patient to continue walking not only during the stage of inflammation, but also long after the ulcer has developed. There is therefore a rapid increase in the size of the ulcer as the infection spreads to deep tissues. Ulcers do not develop in patients with high foot pressures but preserved pain perception, as is the case in rheumatoid arthritis, because the pain caused by the inflammation will force them either to change their usual gait pattern and redistribute the high pressures or, alternatively, to rest their foot until the inflammation has subsided.[3]

Painless joint injury and subsequent extensive use of the limb lead to disintegration and dislocation of the joint (Charcot joint). The most commonly affected joints are the tarsometatarsal joints followed by the metatarsophalangeal joints. The foot arch may collapse, resulting in the rocker-bottom deformity that is associated with areas of high pressure in the midfoot.

Peripheral vascular disease is 20 times more common in diabetic patients than in the general population and often coexists with neuropathy. It usually has the same clinical presentation as in nondiabetic patients. The femoropopliteal segments are most often affected, but the smaller vessels below the knee are more severely affected in patients with diabetes than in those without.[4] Another feature of diabetes is loss of the sympathetic tone in small vessels due to autonomic neuropathy, which results in increased arteriovenous shunting, as evidenced by the presence of a raised venous Po_2 in the absence of peripheral vascular disease.[5] The existence of medial arterial classification, finally, makes the noninvasive evaluation of the ischemic disease difficult as it can yield misleadingly high results during Doppler investigations.[6]

Limited joint mobility, probably caused by nonenzymatic glycosylation of the collagen, is another potential etiopathogenic factor, and in recent studies it has been shown to be related to high foot pressure and ulceration in diabetic patients with neuropathy.[7] The "prayer" sign is a simple clinical finding for detecting limited joint mobility. Finally, leukocyte function may be impaired in patients with diabetes, resulting in a reduction of defenses against invading microorganisms.[8]

Foot ulceration may be the presenting feature that leads to the diagnosis of diabetes and of other long-term complications. The case history in Gavin's excellent presentation elsewhere in this issue is characteristic of this situation.[9] The patient had significant peripheral neuropathy and proliferative retinopathy when the diabetes mellitus was first diagnosed. Back in 1975, Walsh and colleagues described a series of similar patients with hitherto-undiagnosed diabetes, severe foot problems, and retinopathy and named the condition "the foot-eye syndrome."[10]

What can we do, then, when confronted with such an ominous situation apart from watching the patient undergo one amputation after the other and even die? The progress of our knowledge of the pathogenesis of foot problems over the past decade has enabled us to develop techniques toward both the prevention and treatment of such problems. The development of special diabetic foot clinics that incorporate the services of diabetologists, podiatrists, nurse educators, and surgeons, both orthopedic and vascular, is probably one of the major achievements over the past two decades, and these have been shown to effectively reduce the number of foot amputations.[11,12]

Prevention and early treatment of foot problems are the main aims of a foot clinic. Pecoraro and associates studied 80 consecutive lower limb amputations in diabetic patients and found that an identifiable and potentially preventable event, mainly minor trauma, triggered a sequence of events that ended in amputation in 86% of the patients.[13] Therefore, early identification of patients at risk using simple techniques that are discussed by Gavin and co-workers is crucial in preventing such catastrophes.[9] Clinical examination and the measurement of the vibration perception threshold and pressure perception threshold using Semmes-Weinstein monofilaments are particularly helpful and can be easily done in a foot clinic by any member of the team.

Education and behavior modification by a nurse educator,

comfortable footwear including socks, insoles, and shoes provided by an orthotist, and general foot health care with callus removal and intensive treatment of minor trauma by a podiatrist are the most important preventive measures and should be provided to every high-risk patient.

Intensive treatment with foot rest, debridement of ulcers, and antibiotic treatment, if needed, under the supervision of diabetologists and surgeons is the first measure when an ulcer develops. The healing potential of a neuropathic nonischemic foot is excellent, and conservative treatment, occasionally requiring local amputations, is usually enough to allow complete healing. The pivotal measure in managing an insensitive plantar foot ulcer is the relief of pressure, which may be achieved by plaster casting.[14]

Considerable progress has also been made over the past years in the management of peripheral vascular disease. As described by Goldstone in this issue, recent developments in microvascular surgery have made it possible to do bypass procedures as far as the dorsal arteries of the foot.[9] Angioplasty is an alternative for those patients in whom an operation is contraindicated or who have local atheromatous disease. The main point that should always be kept in mind is that no patient should undergo a major amputation before there is a proper vascular evaluation, including, if indicated, angiographic studies.

Do we need foot pressure measurements in all high-risk diabetic patients with foot problems? As discussed by Stess, such measurements may be important in the management of diabetic patients with specific problems.[9] The existence of abnormally high foot pressures is strongly predictive of plantar foot ulceration. In a recent prospective study, 35% of all diabetic patients with high foot pressures and 45% of neuropathic patients had the development of an ulcer over a mean period of 30 months, whereas no ulcers developed in patients with normal baseline measurements.[15] Foot pressure measurements are also helpful in the development of new techniques that can offer pressure reduction and redistribution under an at-risk foot.[16]

Despite the aforementioned advantages, the regular use of foot pressure measurements in daily clinical practice is not generally feasible. The equipment is relatively expensive, and the results of pressures measured by different methods are not comparable.[17] On the other hand, clinical examination may provide valuable information: callus is invariably formed under the high pressure areas, indicating local pressure. Simple, inexpensive, semiquantitative techniques such as the Harris mat may also be helpful if access to more advanced equipment is not available.

Therefore, the message to diabetic patients who worry about possible future foot problems should be an optimistic one. Limb amputation is not an inevitable fact of diabetes; on the contrary, it is the most preventable of the long-term diabetic complications. With their cooperation and a multidisciplinary approach, a dramatic reduction of major limb amputations can be achieved.

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The Los Angeles Riots and the Medical Profession

AT FIRST GLANCE there appears to be little connection between the medical profession and the recent Los Angeles, California, riots other than the obvious: 58 lives lost, 2,000 injured, and destruction of property, including clinics and physicians' offices. And perhaps Tim Rutten's interpretation of events as a "new" kind of riot is not entirely accurate (T. Rutten, "A New Kind of Riot," *The New York Review of Books,* June 11, 1992, pp 52-54). Still, events in Los Angeles struck me as containing a possible lesson about the dangers of consumerism for our stressed profession.

According to Rutten, the collapse of urban democracy in Los Angeles, "a rigidly segregated, bewilderingly diverse city," evidenced by the three days of riots starting April 30, 1992, followed from high unemployment, exploitative practices of local businesses where profits added little to the worth of the community, a belief system rooted in the chaos of commercials, and a police force literally out to lunch once the action started.

The medical profession, also an organization of bewildering diversity and rigid segregation, increasingly expresses similar social dynamics to those found in south-central Los Angeles. A useful comparison of the two communities, disparate as the populations may seem, can be ventured.

The south-central Los Angeles community of African Americans, Hispanics, Asian Americans, and whites suddenly found itself without four primary elements that all social organizations must supply their members: work, a commercial network of exchange, a binding belief system, and controlling civic power. The community included many unemployed persons without hope of obtaining work, the chaos of television commercials aggravated an offended

sense of individualism, and, once challenged, the police withdrew. A blend of diverse ethnic groups came together in an extreme example of a new American public displaying the ultimate in consumerism: "The Final Fire Sale—Nothing Down and Forever to Pay."

When the medical profession is held against the same template, the picture differs in degree but not in substance. Of course we have and provide work, but we presently exclude 37 million Americans from "working" on their own health. We have a binding belief system of service to the sick that is unraveling under a perverse philosophy of consumerism. Our civic control, both internal and external, is devolving from reasoned collaboration into malignant confrontation.

While all thinking citizens want constructive action to heal the wounds and avoid future riots, currently there is little reason for hope. Whether in Los Angeles or in medical care issues, federal and state politicians will make noise about what should be done, then ineptly distribute billions of dollars. In Los Angeles, scapegoats will be found and displayed on television screens across the nation, while it is said that "those people" should get their acts together and that the nation does not need to make major changes. In short, more and more people will receive an education in the new American way: expecting more than is possible and more than you pay for.

The point for the medical profession is that we carry the potential for trouble. While unlikely to result in riots, it is every bit as crippling as we become the target, deservedly or not, of public outrage. The ambiance of goodwill that has sustained the medical profession for so long is not standing up against the inroads of consumerism. The corporate pressure to continually increase the appetite of a targeted population erodes any sense of personal loyalty or lasting commitment between patient and physician.

Dr Madison Richardson's comments are useful to bring into focus the lesson of the riots for the medical profession. A black surgeon born, reared, and practicing in south-central Los Angeles, Dr Richardson succinctly summarized his three days' service in the emergency department at Daniel Freeman Memorial Hospital during the riots: "All of this is about dignity, not having a job, coming from a broken family and all the drugs, that is one thing; and that's ultimately what makes you know that something is going to erupt, and [that] is exactly what happened" (W. Hearn, "Riot Medicine in Shades of Black and White," *American Medical News*, June 1, 1992, p 3).

Dr Richardson's diagnosis of the rage that exploded into the Los Angeles riots as a case of indignity leads to the question whether the medical profession is conveying dignity to our patients and community. Not a commodity from the consumer world, dignity lies in the circumstance of being recognized, understood, and listened to as an autonomous person. Dignity is the consequence of a direct human interaction that has considerable to do with a shared sense of freedom and little to do with money and power.

Do we, for dignity's sake, ensure that every person in the nation can work and contribute to his or her own health, not just the 85% of the people with insurance? In the business of medicine, do we ensure added wealth and worth to our community and not to our investment portfolios? Do we listen to the public's voice to ensure that we reinforce a patient's dignity through our advocacy? When we can answer yes to each of these questions, we have a strong beginning to a possible treatment plan for Dr Richardson's diagnosis writ large.

Equally important for our success is a reasoned and accepted set of self-imposed expectations and beliefs, a unifying philosophy. Patently, the Hippocratic Oath no longer suffices. Nor does a statement of professional ethics make much sense in binding us together to the immense task of serving an outraged public.

To achieve an explicit, unifying philosophy, we must begin by listening to each other and asking what we are about as a profession. We weaken not because we are specialized, speaking different languages of science, but because we are losing our center of belief in ourselves as agents of healing.

Granted, we live in confusing times. Granted, we face an explosion of medical knowledge. Granted, we live with diminishing resources. Granted, we are confronted with intractable medical and social issues. This is no time to despair, however. Beware the empty voice of "I'll get mine while I can." Listening carefully to colleagues, we can address difficult realities and must do so if we are to regain our position of trust.

Physicians need to reaffirm their belief in the spirit and work of men and women of goodwill. No matter how unpopular it may sound, we need to say, and say repeatedly, that things—commercial things, quick cures—do not bring health. We need to declare a philosophy that the pursuit of health demands a common dedication by patient, physician, and community. Health is not a coincidence. It is the reward of reasoned, accepted discipline joined with compassionate care and committed concern.

In simple language, we need a unifying philosophy that points the path to health, individual and community, through shared dignity. Only then can all the tests, salves, lotions, pills, prescriptions, procedures, operations, and advice bring about genuine healing. That is the lesson the Los Angeles riots have for us.

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The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Global Health

To the Editor: Sadly, a large proportion of the world's population can never hope to enjoy good health, however it is defined. War, dispersal, famine, disease, ignorance, and prejudice stifle any chance of normal physical and mental development for countless men, women, and children. The totality of unnecessary misery is overwhelming.

More than most people, physicians, nurses, and other health professionals can be expected to be sensitive to such a depth of suffering, wherever it is found and whatever the causes. They may well claim, however, that the many gross inequalities and injustices that defeat the best efforts of government leaders, politicians, and economists are far beyond the skills of the healing professions to alleviate. Entry into our professions comes only after years of study, which we must continue throughout our careers, and the demands of practice, teaching, and research are virtually open-ended. So most physicians may reasonably feel that the welfare of their own patients and the needs of the next generation of physicians exhaust all the energy and empathy they have available.

Nevertheless, the situation of hundreds of millions of fellow inhabitants of this island, Earth, remains undeniably intolerable and unacceptable. It is capable of improvement, without great expense, if the will exists. And the medical profession, worldwide, has a huge, largely unawakened potential for securing improvements in basic health, which in turn will increase self-help, economic independence, and social stability.

Action in International Medicine (AIM) was set up in 1988 to raise this potential among the health professions. An international charitable foundation, AIM is registered legally in the United Kingdom. So far (September 1992) it has attracted the support of 97 member institutions (colleges, academies, universities, schools, associations) based in 32 countries. It is also incorporated in the United States, with tax-exempt status. There is an international advisory panel composed at present of 40 eminent medical people representing 21 countries who are busy developing Forums of Global Health to encourage regional and national initiatives. The *AIM Bulletin* is published quarterly. It is probably no exaggeration to claim that a critical global mass of commitment has been achieved.

In AIM, we are convinced that we should deploy our uniquely extensive, varied, and prestigious membership to help all countries, poor or industrialized, to accomplish one particular priority: access by all people to a system of primary health care that includes the center, clinic, or hospital of first referral. Such a system can only be sustainable and capable of improvement if the health professionals involved can rely on their own reasonable domestic, educational, and financial needs being met regularly within local resources and with due regard to cultural sensitivities. They must be able to achieve self-respect and pride in their contributions to this crucial basis of national health care. It is not a glamorous or emotional concept, but without the primary infrastructure, neither secondary nor tertiary specialist care, often so desperately needed, can hope to become established in national or community health from one generation to another.

Those involved in AIM fervently wish to promote a commonwealth or fellowship of the health professions both within any one country and, more important, throughout the world. No one doing medical work of any kind should be allowed to feel isolated or alone. Every contribution is of value.

In my original concept of a wholly professional world health service (*Ciba Foundation Symposium Health of Mankind*, published by Churchill, London, 1967), the most urgent need appeared to be to provide clinical skills and teaching where none existed. This need continues in many deprived areas, and we readily join with other oganizations in efforts to meet it, but we have decided that AIM's own road is to make available those clinicians, teachers, organizers, and managers, all highly experienced in one or more developing countries, who can guide and assist local professionals to strengthen permanently their own appropriate health systems. Action in International Medicine's strength is multidisciplinary and intersectoral. When funds permit, we try to respond to appeals for help by sending teams consisting not only of a physician but also a nurse, teacher, manager, planner, and environmentalist, or other appropriate mix. Their task is to analyze the problems, recommend changes, assist in transformation, and later evaluate and modify as necessary. In this way, comparatively small sums of money can catalyze enduring changes for the better.

Readers of The Western Journal of Medicine are urged to join us in commitment and in action, through their institutions or as individuals. Constructive criticism and helpful suggestions would also be welcome.

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Lessons From the Practice

Dear John

MARGARET WATKINS, MD, *Boise, Idaho*

The birthday card has a large duck on the front and a caption appropriate for a little guy celebrating his first. As I address the envelope in care of his parents, I am suddenly struck by a poignant flashback to John's first weeks of life.

John weighed only 920 grams at birth. He arrived 13 weeks ahead of schedule and 120 miles away from our newborn intensive care unit. I received the call about his untimely arrival amidst the hassles of a busy unit and our annual perinatal meeting. I rather irritably grumbled about "another transport" and borrowed enough change to make a long distance call from the pay phone in the foyer of the conference center to John's rather distraught referring physician. Stabilization procedures were conveyed and more borrowed money and phone calls marshalled our transport team.

It seemed forever before I received a progress report from the team, and when John finally arrived in the middle of the night, I was already dead-dog tired and annoyed at the lateness of the hour. My disgruntled demeanor changed instantly at the sight of this tiny human being as if I had not seen thousands of premature infants in my career. He looked somewhat like a baby bird, with soft blond lanugo covering his body and a remarkable mop of reddish orange hair. He was attached to ventilator tubing, monitors, and intravenous lines and appeared unequally mated with technology.

The next six weeks of John's life were a matter of endurance and perseverance. At 700 grams he was subjected to ligation of a patent ductus arteriosus and weathered this like a true champion. After 38 days, he was finally off the ventilator and could enjoy his mother's milk from the distance of a transpyloric tube.

I remember well the day John got off oxygen. He was an "old man" of 61 days and weighed a whopping 1,984 grams (4 lb 6 oz). The respiratory therapist made a sign for him, placed over the doorway to his room, saying "Look, Ma! No Os." He and I took a walk around the nursery, visiting all his roommates. When he went home at 72 days of age, he weighed 2.3 kg (4 lb 14 oz) and still had hair the color of shredded carrots. His mother cried. So did we. We were paradoxically elated and saddened; it seemed that a part of us was missing.

What was it about John that makes me remember him so vividly out of the hundreds of "premies" admitted to our unit every year? Perhaps it was his remarkable constitution. Perhaps it was his parents who sat by his bedside for hours, reading poetry and Shakespeare to him. Their quiet attentiveness and unwavering faith moved us deeply. Their cheerful and unconditional confidence in our ability to care for their son was humbling. Perhaps it was because he was graced with a hairdo that caught everyone's eye and that still flourishes in recent pictures. Deep down, I know I remember him so well because his valiant struggle for survival epitomized all the right reasons I went into this subspecialty in the first place.

"Dear John, we thought you were beautiful on that first night, covered as you were with electronic devices, monitors, tape, and tubes. Our feelings were reinforced by your tenacity and the quiet courage of your family. Today, as a happy, healthy toddler, you're more lovely than ever."

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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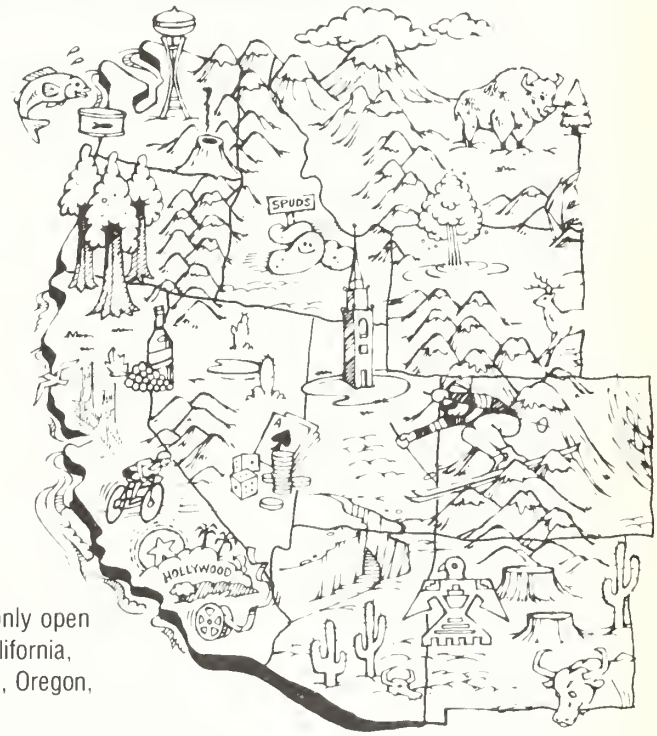

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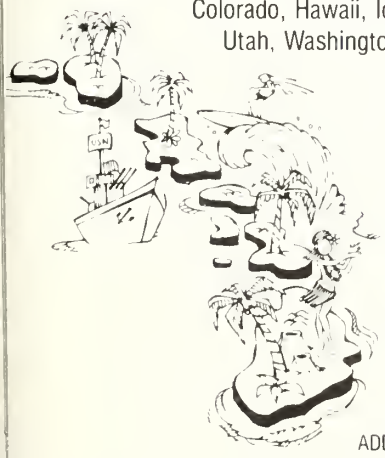

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ABSTRACTS JANUARY 1993

(Wilson MJ, Marelich WD, Lemp GF, et al: HIV-1 seroprevalence among women attending sexually transmitted disease clinics in California. West J Med 1993 Jan; 158:40-43)

To evaluate the distribution of the human immunodeficiency virus type 1 (HIV-1) epidemic among California women, we analyzed HIV-1 seroprevalence and risk factors among women attending sexually transmitted disease (STD) clinics in 21 local health jurisdictions. Using standardized protocols developed by the Centers for Disease Control, we tested unlinked serum specimens from women attending participating STD clinics in 1989. We analyzed demographic characteristics, HIV risk exposure groups, and results of HIV-1 antibody testing on 17,210 specimens with an overall HIV-1 seroprevalence of 0.57%. Seroprevalence rates were highest for African-American women, women 25 to 29 years of age, injection drug users, and women attending STD clinics in San Francisco. After multiple logistic regression analysis, HIV-1 seropositivity remained highest for these four groups. The rate of HIV-1 infection among women attending STD clinics in California underscores the continued need to make HIV counseling and testing an integral component of routine services for women being evaluated for, or presenting with, sexually transmitted diseases.

SEXUALLY TRANSMITTED DISEASES HIV INFECTION AMONG WOMEN
HIV-SEROPREVALENCE

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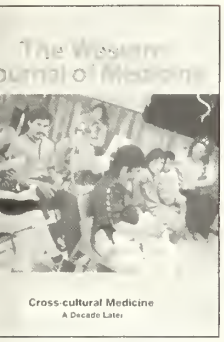

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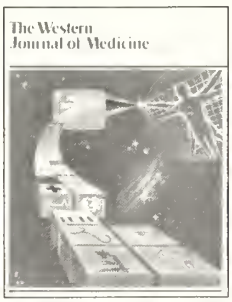

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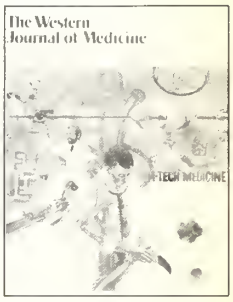

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(Continued from Page 22)

February 28-March 5—**ENT Ski Conference.** University of Nebraska Medical Center Continuing Medical Education Program at Keystone Resort, Keystone. Sun-Fri. Contact: Brenda C. Ram, University of Nebraska Continuing Education, (402) 559-4152.

February 28-March 5—**7th Annual Cardiology for the Clinician: Practical Guidelines for Merging Advances in Cardiology With Bedside Medicine.** University of Illinois at Snowmass. Sun-Fri. Contact: Sue Talbert, UIC Conferences and Institutes (M/C 607), Box 6998, Chicago, IL 60680. (312) 996-4631.

March DTBA—**Fifth Annual Colorado Geriatrics Overview.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. Contact: U of Colo.

March 7-10—**XXVII Aspen Conference on the Fetus and Newborn.** Children's Hospital at Aspen. Sun-Wed. Contact Jessica White, (303) 861-6946 or (800) 225-0010.

March 12-13—**Moms at Risk/Babies at Risk.** Children's Hospital at Greeley. Fri-Sat. Contact: Mary Haley, (303) 861-6946 or (800) 225-0010.

April 1-3—**Rural Perinatal Traineeship Program.** Children's Hospital at Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

April 6-7, 13-14—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 861-6668.

April 22-24—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

April 26-27—**Neonatal Resuscitation Hospital-based Instructor Course.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6668.

May 7-8—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack, (303) 861-6506.

May 10-13—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6188.

June 10-11—**Basic/Advanced Fetal Monitoring Program.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Trish Beachy, (303) 270-8376.

June 10-11—**Neonatal Resuscitation Program Provider Course.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Outreach Office, (303) 861-6668.

June 10-12—**Sixth Annual Summer in the Mountains Conference.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Sat. Contact: Mary Haley, (303) 270-8376.

June 14-16—**Community Health Traineeship Program.** Children's Hospital, Denver. Mon-Wed. Contact: Outreach Office, (303) 861-6668.

July 13—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

IDAHO

February 19-21—**Ada County Medical Society's 34th Annual Medical Winter Clinics—"Sandbox Summit"—A Potpourri of Pediatric Pearls.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, Idaho Medical Association members; $175, non-members. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930, or Marie Chester, (208) 386-2135.

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 15-16—**23rd Annual Winter Pediatric Orthopaedic Seminar.** Hilton Hotel, Albuquerque. Fri-Sat. Contact: Shirley R. Hagan, Carrie Tingley Hospital, 1127 University Blvd NE, Albuquerque 87102. (505) 272-5214 or (800) 472-3235.

February 26-27—**21st Annual New Mexico Thoracic Society Lung Disease Conference.** Kachina Lodge, Taos. Fri-Sat. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

March 13-14—**Pediatric Emergency Medicine: The Wylder Lectures.** W. R. Lovelace II Education Center, Albuquerque. Sat-Sun. Contact: Steven Yabek, MD, 715 Grand Ave NE, Ste 207, Albuquerque 87102. (505) 848-3700.

May 14-15—**New Mexico Medical Society Annual Meeting.** Society Office, Albuquerque. Fri-Sat. Contact: NMMS, 7770 Jefferson, Ste 400, Albuquerque 87109. (505) 828-0237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

January 14—**Pediatric Topic.** Thurs. Contact: UOS.

January 24-27—**Midwinter Conference on Chest Disease.** ITS at Snowbird. Sun-Wed. Contact: ITS.

January 26-30—**Craniofacial/Oculoplastic Surgery.** UUSM at Cliff Lodge, Snowbird. Thurs-Sat. 21 hrs. $475. Contact: UUSM.

February 8-12—**Advances in Internal Medicine.** UUSM at Snowbird, Mon-Fri. Contact: UUSM.

February 8-12—**Surgical Pathology.** UUSM at Yarrow Hotel, Park City. Mon-Fri. 20 hrs. $495. Contact: UUSM.

February 12-13—**Utah Ophthalmology Society—Annual Winter Ski Meeting—Ski '93.** Fri-Sat. Contact: UOS.

February 13-20—**Update in Clinical Microbiology and Immunology.** UUSM at Yarrow Hotel, Park City. 1 wk. 25 hrs. $435. Contact: UUSM.

February 19-23—**37th Anesthesiology Update: Anesthesia and the Nervous System.** UUSM at Snowbird Cliff Lodge. Fri-Tues. 20 hrs. $500. Contact: UUSM.

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February 23-27—**Physical Medicine and Rehabilitation Update.** UUSM at Prospector Square Conference Center, Park City. Tues-Sat. 16 hrs. $350. Contact: UUSM.

February 25-27—**Pediatric Update.** UUSM at Jackson, Wyoming. Thurs-Sat. $175. Contact: UUSM.

February 28-March 3—**34th Annual OB/GYN Update.** UUSM at Yarrow Hotel, Park City. Sun-Wed. 13 hrs. $375. Contact: UUSM.

March 3-6—**Maternal Fetal Medicine Update Course.** UUSM at Yarrow Hotel, Park City. Wed-Sat. 13 hrs. $375. Contact: UUSM

March 8-12—**Microsurgery Workshop.** UUSM at University Park Hotel, Salt Lake City. Mon-Fri. 30 hrs. $1,900. Contact: UUSM.

March 8-12—**Advances in Internal Medicine.** UUSM at Cottonwood Center, Snowbird. Mon-Fri. 20 hrs. $375. Contact: UUSM.

March 12-13—**Western Intermountain Neurological.** UUSM at University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

March 23-26—**Family Practice Refresher Course.** UUSM at Salt Palace, Salt Lake City. Tues-Fri. 27 hrs. $450. Contact: UUSM.

April 2—**Nephrology and Hypertension.** UUSM at University Park Hotel, Salt Lake City. Fri. 7 hrs. $50. Contact: UUSM.

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Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 15-17—**WTS Chest Conference and Lung Day.** Leavenworth. Fri-Sun. Contact: Washington Thoracic Society, (206) 441-5100.

January 21—**Law and Medicine Symposium.** Seattle. Thurs. Contact: PCMS CME.

January 21-22—**Alzheimer's Update.** Seattle. Thurs-Fri. Contact: U/W.

January 27—**Oncology Update.** Tacoma. Tues. Contact: Multicare, (206) 594-1221.

January 29—**Psycho-social and Neuropsychiatric Aspects of AIDS.** Seattle. Thurs. Contact: U/W.

February 3—**HIV Infections.** Tacoma. Wed. Contact: PCMS CME.

February 4-6—**Mt. Bachelor—CME.** Bend, Oregon. Thurs-Sat. Contact: PCMS CME.

February 11—**Managing Occupational Health and Safety Programs.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

February 12—**General Surgery Review.** Everett. Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

February 19—**Healthcare Economics in the '90s.** Seattle. Fri. Contact: VMMC.

February 26—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

February 26-27—**Gastroenterology Update.** Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine, (509) 448-2513.

March 2—**Health Effects of Noise Exposure.** Seattle. Tues. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 3-6—**North Pacific Pediatric Society.** Seattle. Wed-Sat. Contact: Children's, (206) 526-2501.

March 11—**Neurotoxicology.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 11-12—**Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 12—**Pulmonary Medicine for the Family Practitioner.** Seattle. Fri. Contact: Children's, (206) 526-2501.

March 15-25—**Physical Medicine and Rehabilitation Review.** Seattle. Mon-Wed. Contact: U/W.

March 19-20—**APLS Course.** Seattle. Fri-Sat. Contact: Washington Chapter, American College of Emergency Physicians.

March 24-26—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

March 26-27—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: Washington Academy of Eye Physicians and Surgeons, (206) 441-9762.

March 31—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

April 6-9—**Family Practice Review.** Arizona. Tues-Fri. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

April 8-9—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

April 9—**Advances in Occupational and Environmental Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

April 16—**20th Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare, (206) 594-1221.

April 16-17—**Tacoma Surgical Club.** Tacoma. Thurs-Fri. Contact: PCMS CME.

April 23—**Terminal/Palliative Care Update.** Tacoma. Fri. Contact: PCMS CME.

April 23-24—**Clinical Allergy for the '90s.** Seattle. Fri-Sat. Contact: VMMC.

April 23-25—**Washington State Physical Therapy Association.** Seattle. Fri-Sun. Contact: Children's, (206) 526-2501.

April 28-30—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Fri. Contact: Washington Chapter, American College of Emergency Physicians, (206) 441-9762.

April 30-May 2—**Radiology Annual Meeting.** Vancouver, BC. Fri-Sun. Contact: Pacific Northwest Radiological Society, (206) 441-9762.

May 7—**Office Gynecology.** Tacoma. Fri. Contact: PCMS CME.

May 7-8—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

May 13—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute, (206) 258-6322.

May 14-15—**Northwest Spine Review Course.** Seattle. Fri-Sat. Contact: VMMC.

May 16-19—**American Thoracic Society.** San Francisco. Sun-Wed. Children's, (206) 526-2501.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety, (206) 543-1069.

(Continued on Page 93)

CONTINUING MEDICAL EDUCATION

(Continued from Page 92)

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare, (206) 592-1221.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

February 18-20—**Wyoming Medical Society—Winter Seminar.** Holiday Inn at Gillette. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

February 25-27—**Pediatric Update.** University of Utah School of Medicine at Jackson. Thurs-Sat. $175. Contact: Univ of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581-8664.

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. ◆

FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

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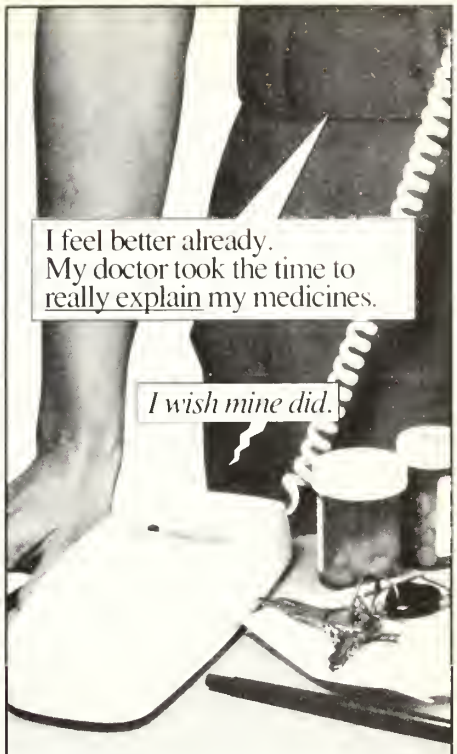

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FAMILY PRACTICE. Premier multispecialty group near Portland, Oregon has two excellent opportunities for BC/BE Family Practitioners. Join one of two satellite clinics in which Family Physicians and Physician Assistants currently practice. Superb lifestyle, abundant recreational opportunities, and generous benefits package. Send CV to Karen Stanton, c/o The Vancouver Clinic, 700 NE 87th Ave, Vancouver, WA 98664.

PRIMARY CARE PHYSICIAN wanted for expanding eastern Washington clinic. Full- and part-time positions available. Located in prime recreational area. Skiing, sailing, fishing, hunting all within a short distance. Enjoy mild climate, excellent schools and a major university branch campus in growing community of 100,000 plus. Challenging work in a superbly equipped clinic with a state-of-the-art lab, x-ray, laser, and endoscopy. Above average compensation and benefits including malpractice, health insurance, and CME. Contact Dr Stephen L. Smith, 310 Torbet, Richland, WA 99352; (509) 545-8340 or FAX (509) 946-7666.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/ Nephrologist/ Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

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YELLOWSTONE NATIONAL PARK. Physician to cover outpatient clinic, emergency room, and inpatient at Lake Hospital from Memorial Day to mid-September 1993. Send CV to Yellowstone Park Medical Services, 707 Sheridan Ave, Cody, WY 82414, or call (307) 578-2461.

BC/BE GENERAL INTERNIST NEEDED. Nine physician department in 27 doctor multispecialty clinic. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403, (800) 234-5637.

PHYSICIANS WANTED

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Physicians needed to join a multispecialty group, partnership, or solo practice, due to the explosive population growth. BC/BE physician specialties:

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- **CARDIOLOGY**
- **PSYCHIATRY**
- **INTERNAL MEDICINE**
- **ORTHOPEDICS**

Excellent practice opportunities offer guaranteed income and a strong referral base.

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AMBULATORY CARE/FAMILY PRACTICE. California Emergency Physicians Medical Group is a partnership of Ambulatory Care and Emergency Medicine specialists. Opportunities available for physicians who specialize in Family Practice. We have facilities in northern, central, and southern California. For more information send CV to John Gravette, 2101 Webster St, #1050, Oakland, CA 94612, or phone (800) 842-2619.

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 105,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- FAMILY PRACTICE
- ORTHOPEDIC SURGERY
- OTOLARYNGOLOGY
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These excellent practice opportunities offer guaranteed income and a strong referral base.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 105,000; a growing area with new businesses and a stable economy. A 30% plus growth in population and jobs is predicted for our area during 1990s.

Located in central California near Sequoia National park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:
Tulare District Hospital
Physician Recruiting Office
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Los Angeles, CA 90009
(800) 468-2687

BC/BE INTERNIST to join busy three Internist group in Bishop, California, gateway to the eastern Sierras. Ideal location to work, live, and enjoy four season activities. Office located adjacent to hospital. Send résumés and inquiries to Joanne Crane, Office Manager, 152 Pioneer Ln, Bishop, CA 93514.

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

CALIFORNIA. Family Physician, BC/BE, sought for San Francisco bay area. Near Santa Cruz Mountains. Join four BC Family Physicians. Compensation potential. Rated top 3% Family Physicians nationwide by consultant. Well organized, busy, independent, small group practice. Contact Pam Creider, Office Manager, c/o Campbell Medical Group, 476 E Campbell Ave, Campbell, CA 95008; phone (408) 378-3100; FAX (408) 378-1610.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, an expanding multispecialty group of 190 plus physicians, needs BC/BE Pediatrics, Internal Medicine, Family Practice, OB/GYN, Urgent Care, General Surgery, Orthopedic Surgery, Urology, and Ophthalmology physicians. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. BE/BC. Call or write Bill De Long; (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

(Continued on Page 95)

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PHYSICIANS WANTED

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Call (800) 727-2478 or FAX your CV in complete confidence to (408) 727-7390. Never a fee to the physician. **Nugent & Grant, 1400 Coleman Ave, Ste B24, Santa Clara, CA 95050.**

CALIFORNIA FAMILY PRACTICE. If you love the ocean, the mountains, a mild climate and want to be within one hour of the city; if you prefer working in an independent group practice where care is first and money is second, please contact Ken Baker, Physician Search Group, 550 Montgomery St, #725, San Francisco, CA 94111; (800) 229-0411; FAX (415) 399-0411.

PRACTICE OPPORTUNITY. GENERAL SURGERY. GENERAL SURGEON DESIRED IN THE PACIFIC NORTHWEST – BC/BE. Pullman Memorial Hospital, located on the Washington State University campus, is a progressive 42-bed Acute Care facility, with a solo or possible partnership opportunity for a General Surgeon. With a service population of 70,000, Pullman Memorial has a full complement of specialties represented in its 65 member medical staff. Pullman, Washington is uniquely located in the center of the Pacific Northwest, bounded on the west by the Snake River as it comes out of the mountains and travels to join the Columbia. The Rockies border to the east. Pullman is renowned for the virtually unlimited sporting, recreational, cultural, and educational opportunities of an urban center in a beautiful, rural setting. For more information on this multi-town opportunity, contact Pullman Memorial Hospital, NE 1125 Washington Ave, Pullman, WA 99163.

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PUGET SOUND–WASHINGTON STATE. ENT independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attn: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

PHYSICIANS

The California Department of Corrections, currently has a number of opportunities available in the following areas:

PROGRAM MANAGER-CHIEF MEDICAL OFFICER
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This is the Lead Manager position for statewide HIV-TB program administration and HIV-ID Training for the entire department.

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Positions are very flexible: full-time, part-time, and contract consultant positions. Up to **$98,000** plus excellent State of California benefits.

For any of the above opportunities, call: **(916) 327-7081**
Or send Curriculum Vitae to: California Department of Corrections, Dept. DHCS, P.O. Box 942883, Sacramento, CA 94283-0001. EOE.
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California Department of Corrections

PHYSICIANS WANTED

BC/BE FAMILY PHYSICIAN to join five physician, two mid-three, mid-level (three Family Practitioners, one OB, one Internal Medicine, one Certified Nurse Midwife, two Physician's Assistants) busy migrant/community clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work and Emergency Room coverage. Excellent relationship with well trained BC Family Practitioners and Surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation up to 32 days per year. Public Health Service immediate loan repayment slot. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

GILROY, CALIFORNIA. BC INTERNIST to join established but growing private practice in Gilroy, California. Ideal candidate will have one to two years practice experience. Guaranteed salary and benefits. Excellent practice opportunity in this growing community. Send CV to Number 272, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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PHYSICIANS WANTED

THINK ABOUT IT!! Arizona needs Primary Care physicians in several underserved areas. From northern plateaus to southern plains, both urban and rural– solo to multispecialty. Great family lifestyle, full benefits, excellent salaries. Write Bill De Long, Catalina Professional Recruiters, PO Box 12650, Tucson, AZ 85732, or call (800) 658-9166.

PUGET SOUND–WASHINGTON STATE. FAMILY PRACTICE independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attn: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

BC/BE FAMILY PRACTITIONER with commitment to caring for the underserved, needed to join one Family Practitioner, Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs and four Family Physicians. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

Ads Get Results!

(Continued on Page 96)

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PHYSICIANS WANTED

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PORTLAND, OREGON

Ideal opportunity. Progressive 450-bed teaching hospital seeks experienced BC Internist to aid in developing private practice model for Internal Medicine Resident Ambulatory education. Half-time devoted to clinical practice and half-time to teaching Internal Medicine Residents in the office setting. Exciting opportunity to reform medical education within an evolving regional healthcare delivery system. Outstanding compensation, benefits, and life-style. Send CV and references to:

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Personnel Service
PO Box 1200
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- Medical Director

If you are committed to excellence and strongly motivated for success, we would like to hear from you. Please send your CV to Ron Scott, San Jose Medical Group, Inc*, 45 S. 17th St, San Jose, CA 95112; **or call (408) 282-7755.**

*An independent physician group affiliated with Stanford University Medical Center.

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(509) 482-2164
FAX: (509) 482-2187

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BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved, needed to join clinics in Milton-Freewater, and Hermiston, Oregon. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

SAN FRANCISCO AREA. Internist/Family Practitioner, full-time or part-time. Established practice; challenge and diversity of private practice. Send CV to Martin Lorber, MD, 901 Campus Dr, Rm 208, Daly City, CA 94015; or call (415) 992-4466.

(Continued on Page 97)

SAINT JOSEPH

New Mexico

Excellent opportunity for board certified or board eligible OB/GYN, Pediatric, Internal Medicine and Family Practice physicians to practice within MED-NET (Medical Network of New Mexico), an integrated health care system. Enjoy sunshine, skiing, hiking, fishing and hunting in a Southwestern lifestyle. For further information contact Anne Winter, Director of Professional Development, The St. Joseph Healthcare System, Albuquerque, New Mexico.

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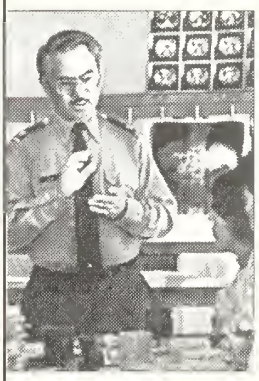

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(Continued from Page 96)

PHYSICIANS WANTED

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ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

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MOUNTAIN VIEW. BC/BE Family Physician to join thriving four member Family Practice group located in the heart of the Silicon Valley. Practice includes Surgery and Obstetrics. C-sections are OK. Excellent salary and benefits. Contact Dianne Higgins, MD, 253 Franklin St, Mt View, CA 94041; (415) 967-5591.

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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Valley Medical Center of Fresno, a Primary teaching hospital for the University of California, San Francisco–Fresno Medical Education Program, seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position. Eligibility for a UCSF academic clinical appointment preferred. The Orthopedic Department at VMC supports a busy level one trauma center and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. Competitive salary and benefits. Central California location offers enjoyable and affordable year-round recreational living with easy mountain and coastal access.

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FAMILY PRACTICE. Seeking Family Practice or General Practice physician for rapidly growing area in northern Arizona – Bullhead City, Arizona/Lauglin, Nevada. Opportunity unlimited. Compensation unlimited. Malpractice and health insurance. Send CV to Bullhead Medical Center, 1648 Highway 95, Bullhead City, AZ 86442, or FAX to (602) 763-1311.

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OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

ASSISTANT PROFESSOR OF MEDICINE. Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington and VA Medical Center seeks an MD scientist, BC in Internal Medicine/Endocrinology with an independent area of research. Preference given to those with demonstrated experience in performing independent research. Personal grant support desirable. Send CV and references by February 1, 1993, to Daniel Porte, Jr, MD, Research Service (151), VA Medical Center, 1660 S Columbian Wy, Seattle, WA 98108. The University of Washington is an Equal Opportunity/Affirmative Action Employer.

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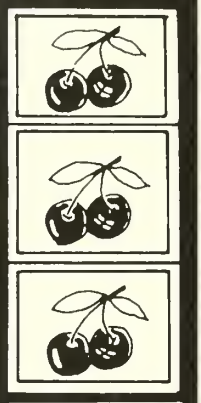

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: February 26-March 3, 1993, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: 1993, date and place to be announced.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: 1993, date and place to be announced.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-15, 1993, Society Office, Albuquerque.

Oregon Medical Association—5210 SW Corbett Ave, Portland 97201. (503) 226-1555. Annual Meeting (House of Delegates only): 1993, date and place to be announced.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: 1993, date and place to be announced.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 10-12, 1993, Jackson Lake Lodge, Moran.

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Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)

Zantac® 300 Tablets
(ranitidine hydrochloride)

Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer.** Most patients heal within 4 weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (e.g., Zollinger-Ellison syndrome and systemic mastocytosis)
4. Short-term treatment of **active, benign gastric ulcer.** Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within 1 or 2 weeks after starting therapy with Zantac 150 mg b.i.d.
6. Treatment of endoscopically diagnosed **erosive esophagitis.** Healing of endoscopically diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with Zantac 150 mg q.i.d. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with Zantac.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer, hypersecretory states, GERD, and erosive esophagitis

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution)

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks
Pregnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed
Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established
Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred
Musculoskeletal: Rare reports of arthralgias
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis

HOW SUPPLIED: Zantac® 150 Tablets (ranitidine HCl equivalent to 150 mg of ranitidine) are peach, film-coated, five-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets

Zantac® 300 Tablets (ranitidine HCl equivalent to 300 mg of ranitidine) are yellow, film-coated, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine per 1 mL in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54)

Store between 4° and 25°C (39° and 77°F). Dispense in tight, light-resistant containers as defined in the USP/NF.

May 1992
2130A

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DIVISION OF GLAXO INC

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Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

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Please see Brief Summary of Prescribing Information on adjacent page.

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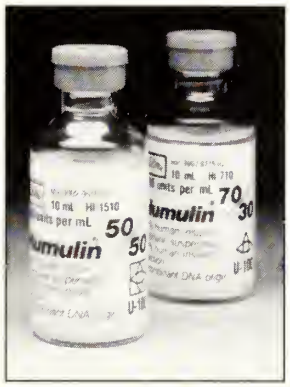

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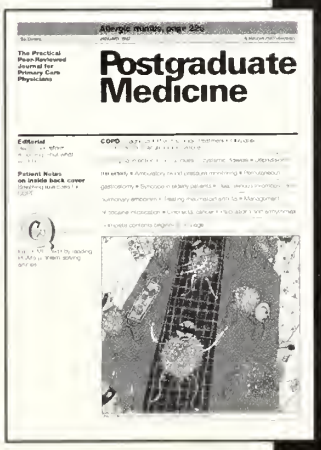

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From the Department of Medicine, Section of Infectious Diseases, San Jose Medical Group, San Jose, and the Department of Medicine, Division of Family and Community Medicine, Stanford University School of Medicine, Stanford, California.

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B. NED CALONGE, MD, MPH; LYLE R. PETERSEN, MD; REBECCA S. MILLER, MS; and GUILLERMO MARSHALL, PhD

From the Colorado Permanente Medical Group, PC, Denver; Centers for Disease Control and Prevention, Atlanta, Georgia; the Center for Studies in Family Medicine, Ambulatory Sentinel Practice Network, Inc; and Department of Preventive Medicine and Biometrics, University of Colorado Health Sciences Center, Denver.

BIOMEDICAL SCIENCE

153 **Blood Coagulation and Its Alterations in Hemorrhagic and Thrombotic Disorders**

SAMUEL I. RAPAPORT, MD

From the Departments of Medicine and Pathology, University of California, San Diego, School of Medicine.

CONFERENCES AND REVIEWS

162 **Interventional Neuroradiology**

STANLEY L. BARNWELL, MD, PhD

From the Charles Dotter Institute of Interventional Therapy, Division of Neurosurgery, Oregon Health Sciences University, Portland.

(Continued on Page 120)

IN HYPERTENSION—

A BALANCE
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The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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ABSTRACTS FEBRUARY 1993

(Shusterman D, Kaplan JZ, Canabarro C: Immediate health effects of an urban wildfire. West J Med 1993 Feb; 158:133-138)

To document the immediate health effects of the urban wildfire that swept through parts of Alameda County, California, on October 20 and 21, 1991, we conducted a retrospective review of emergency department and coroner's records. Nine hospitals (6 local and 3 outlying) were surveyed for the week beginning October 20, 1991. Coroner's reports were reviewed for 25 identified fire-related deaths. A total of 241 fire-related emergency encounters, including 44 inpatient admissions, were recorded for 227 persons. Nearly a fourth of emergency department patients were seen for work-related injuries, more than half of which occurred among professional firefighters. Smoke-related disorders constituted more than half of all emergency department cases; of these, 61% had documented bronchospasm. Major trauma and burns contributed 1% and 4% of principal diagnoses, respectively; these were exceeded in number by corneal abrasions (13%), other medical problems (8%), and minor trauma (7%), among other diagnoses. All coroner's cases involved extensive burns, many with documented smoke inhalation injury. While the Oakland-Berkeley fire storm resulted in a high case-fatality ratio among major burn cases (25/31), those who survived the initial fire storm did well clinically. Among emergency department patients, medical (particularly smoke-related) disorders outnumbered traumatic presentations by a ratio of more than 2 to 1.

WILDFIRE
BURNS
SMOKE INHALATION
URBAN WILDFIRE

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To document the immediate health effects of the urban wildfire that swept through parts of Alameda County, California, on October 20 and 21, 1991, we conducted a retrospective review of emergency department and coroner's records. Nine hospitals (6 local and 3 outlying) were surveyed for the week beginning October 20, 1991. Coroner's reports were reviewed for 25 identified fire-related deaths. A total of 241 fire-related emergency encounters, including 44 inpatient admissions, were recorded for 227 persons. Nearly a fourth of emergency department patients were seen for work-related injuries, more than half of which occurred among professional firefighters. Smoke-related disorders constituted more than half of all emergency department cases; of these, 61% had documented bronchospasm. Major trauma and burns contributed 1% and 4% of principal diagnoses, respectively; these were exceeded in number by corneal abrasions (13%), other medical problems (8%), and minor trauma (7%), among other diagnoses. All coroner's cases involved extensive burns, many with documented smoke inhalation injury. While the Oakland-Berkeley fire storm resulted in a high case-fatality ratio among major burn cases (25/31), those who survived the initial fire storm did well clinically. Among emergency department patients, medical (particularly smoke-related) disorders outnumbered traumatic presentations by a ratio of more than 2 to 1.

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WILDFIRE
BURNS
SMOKE INHALATION
URBAN WILDFIRE

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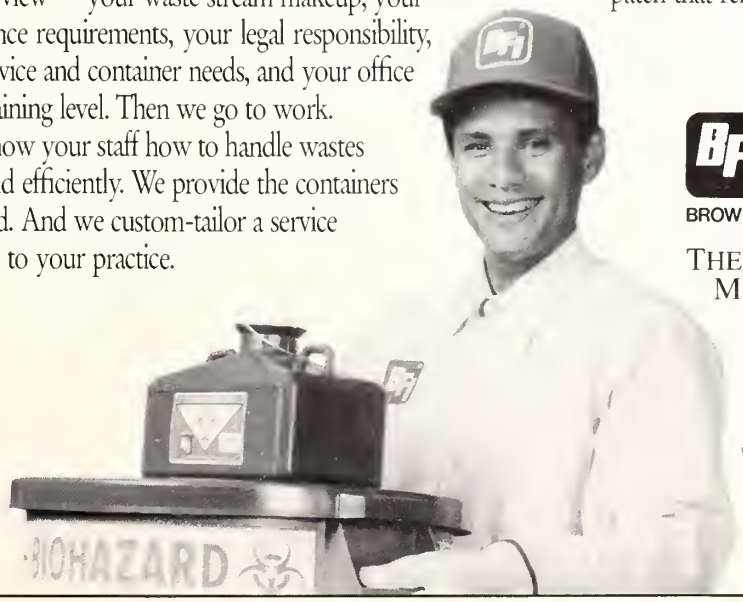

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In Memoriam

California Medical Association

Beebe, Irvin J., San Jose. Died Oct 27, 1992, aged 89. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1932. Licensed in California in 1941. Dr Beebe was a member of the Santa Clara County Medical Association.

Berk, Arnold D., Palm Springs. Died Jun 29, 1992, aged 56. Graduate of University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, 1962. Licensed in California in 1971. Dr Berk was a member of the Riverside County Medical Association.

Bosonetto, Theodore L., Bakersfield. Died Nov 25, 1992, aged 72. Graduate of Indiana University School of Medicine, 1942. Licensed in California in 1952. Dr Bosonetto was a member of the Kern County Medical Society.

Bunch, Rollin F., Oakland. Died Nov 23, 1992, aged 81. Graduate of Rush Medical College, Chicago, Illinois, 1937. Licensed in California in 1949. Dr Bunch was a member of the Alameda-Contra Costa Medical Association.

Centrone, Patrick A., Hemet. Died Sep 6, 1992, aged 83. Graduate of Tufts University School of Medicine, 1935. Licensed in California in 1949. Dr Centrone was a member of the Orange County Medical Association.

Doherty, William R., Palm Desert. Died Sep 19, 1992, aged 72. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1956. Licensed in California in 1967. Dr Doherty was a member of the Riverside County Medical Association.

Filante, William J., San Rafael. Died Dec 8, 1992, aged 63. Graduate of University of Minnesota Medical School, Minneapolis, 1950. Licensed in California in 1952. Dr Filante, a California Assemblyman, was a member of the Marin Medical Society.

Humphrey, Harvey A., San Diego. Died Dec 1, 1992, aged 73. Graduate of Yale University School of Medicine, New Haven, Connecticut, 1944. Licensed in California in 1952. Dr Humphrey was a member of the San Diego County Medical Society.

Jeong, Bessie Y., Oakland. Died Nov 21, 1992, aged 92. Graduate of Medical College of Pennsylvania, 1932. Licensed in California in 1934. Dr Jeong was a member of the Alameda-Contra Costa Medical Association.

La Mont, John M., Seal Beach. Died Aug 27, 1992, aged 48. Graduate of State University of New York, Brooklyn, 1970. Licensed in California in 1971. Dr La Mont was a member of the Orange County Medical Association.

Leong, Henry S., Dinuba. Died Nov 7, 1992, aged 84. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Leong was a member of the Tulare County Medical Society.

Levine, Ira C., Newport Beach. Died Oct 20, 1992, aged 39. Graduate of Harvard Medical School, Boston, Massachusetts, 1977. Licensed in California in 1982. Dr Levine was a member of the Orange County Medical Association.

McClure, Bruce B., San Diego. Died Oct 4, 1992, aged 61. Graduate of Northwestern University Medical School, Chicago, Illinois, 1957. Licensed in California in 1959. Dr McClure was a member of the San Diego County Medical Society.

Mathes, Larry B., San Clemente. Died May 16, 1992, aged 71. Graduate of University of Southern California, 1944. Licensed in California in 1944. Dr Mathes was a member of the Orange County Medical Association.

Minor, Winston D., San Diego. Died Oct 24, 1992, aged 65. Graduate of University of Iowa College of Medicine, Iowa City, 1953. Licensed in California in 1954. Dr Minor was a member of the San Diego County Medical Society.

Mitchell, Sidney P., Palo Alto. Died Nov 22, 1992, aged 79. Graduate of Stanford University, Stanford, California, 1938. Licensed in California in 1938. Dr Mitchell was a member of the Santa Clara County Medical Association.

Morton, Paul V., San Jose. Died Dec 10, 1992, aged 82. Graduate of McGill University Faculty of Medicine, Montreal, 1940. Licensed in California in 1941. Dr Morton was a member of the Santa Clara County Medical Association.

Nagel, Gunther W., San Francisco. Died Nov 17, 1992, aged 98. Graduate of Stanford University, Stanford, California, 1921. Licensed in California in 1921. Dr Nagel was a member of the San Francisco Medical Society.

Newbold, Milton W., Lodi. Died Dec 6, 1992, aged 72. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1944. Licensed in California in 1945. Dr Newbold was a member of the San Joaquin County Medical Society.

Payne, John H., Garden Grove. Died Aug 26, 1992, aged 63. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Payne was a member of the Orange County Medical Association.

Pedemont, Leo R., Oakland. Died Nov 13, 1992, aged 80. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1943. Licensed in California in 1943. Dr Pedemont was a member of the Alameda-Contra Costa Medical Association.

Peterson, H. Harvey, Oakland. Died Dec 10, 1992, aged 73. Graduate of University of Utah College of Medicine, Salt Lake City, 1946. Licensed in California in 1951. Dr Peterson was a member of the Alameda-Contra Costa Medical Association.

Renner, G. Edwin, Concord. Died Nov 23, 1992, aged 57. Graduate of University of California College of Medicine, Irvine, 1964. Licensed in California in 1966. Dr Renner was a member of the Alameda-Contra Costa Medical Association.

Runyon, Leslie A., Castro Valley. Died Aug 8, 1992, aged 83. Graduate of University of Southern California, Los Angeles, 1935. Licensed in California in 1935. Dr Runyon was a member of the Alameda-Contra Costa Medical Association.

Silva, Raoul E., San Francisco. Died Oct 25, 1992, aged 71. Graduate of Universidad Nacional Autonoma de Mexico, 1947. Licensed in California in 1952. Dr Silva was a member of the San Francisco Medical Society.

Stephens, George S., Castro Valley. Died Nov 5, 1992, aged 80. Graduate of Northwestern University Medical School, Chicago, Illinois, 1947. Licensed in California in 1948. Dr Stephens was a member of the Alameda-Contra Costa Medical Association.

New Mexico Medical Society

Brichta, Louis F., Santa Fe. Died Dec 5, 1992, aged 49. Graduate of Baylor College of Medicine, Houston, Texas, 1969. Licensed in New Mexico in 1980. Dr Brichta was a member of the Santa Fe County Medical Society.

Dorn, Ronald V., Jr, Albuquerque. Died Nov 2, 1992, aged 70. Graduate of Marquette University, Milwaukee, Wisconsin, 1946. Licensed in New Mexico in 1953. Dr Dorn was a member of the Greater Albuquerque Medical Association.

Kellner, Robert, Albuquerque. Died Nov 15, 1992, aged 70. Graduate of Charles U. Czech, Liverpool, England, 1957. Licensed in New Mexico in 1969. Dr Kellner was a member of the Greater Albuquerque Medical Association.

Pressman, Ann E., Albuquerque. Died Dec 10, 1992, aged 58. Graduate of New York University, Bellevue Medical School, 1960. Licensed in New Mexico in 1970. Dr Pressman was a member of the Greater Albuquerque Medical Association.

Rico, Joaquin N., Clovis. Died Oct 22, 1992, aged 54. Graduate of Montevideo, Uruguay, 1938. Licensed in New Mexico in 1989. Dr Rico was a member of the Curry-Debaca-Roosevelt County Medical Society.

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ALLERGY/IMMUNOLOGY

May 7-8—**Asthma and Allergy in the 1990s.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 10 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

ANESTHESIOLOGY

March 19-23—**67th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Diego Marriott Hotel & Marina, San Diego. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131-2553. (216) 642-1124.

March 26-28—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort, Dana Point. Fri-Sun. 9 hrs. $175-$245. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

May 23-28—**Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

February 19-20—**Arrhythmias: Interpretation, Diagnosis and Management.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 11-13—**3rd Annual Symposium on Coronary Stenting: A Live Demonstration Course.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 26-27—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 2-3—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Le Meridien Hotel, San Diego. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 23-24—**Coronary Heart Disease Update.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

May 7-8—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Parc 55 Hotel, San Francisco. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

CARDIOVASCULAR DISEASE

March 26-28—**Thromboembolic and Primary Pulmonary Vascular Disease: Diagnosis and Management.** UCSD at Sheraton Harbor Island Hotel, San Diego. Fri-Sun. 18 hrs. $500. Contact: Shirley Kolkey, 9606 Tierra Grande, #106, San Diego 92126. (619) 271-6673.

June 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marriott Hotel, Monterey. Fri-Sun. 12 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 25-26—**Advances in Vascular Diseases.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

July 20-24—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation and UCSD at UCSD Campus, San Diego. Tues-Sat. 36 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-31—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $435. Contact: James Graham, MD, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

EMERGENCY MEDICINE

February 20-27—**Update: Controversies in Emergency and Primary Care.** American Institute of Postgraduate Education at Royal Lahaina Resort, Maui, Hawaii. 1 week. 21 hrs. $450. Contact: Edith Bookstein, PO Box 2586, La Jolla 92038. (619) 454-3212.

February 21-26—**Emergency Medicine: 1993.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Fri. 25 hrs. $465. Contact: UCD.

March 7-12—**13th Annual Mammoth Mountain Emergency Medicine Ski Conference.** American College of Emergency Physicians at Mammoth Lakes. Sun-Fri. 18 hrs. $395. Contact: Daniel Abbott, MD, PO Box 52-B, Newport Beach 92662. (714) 650-4156.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

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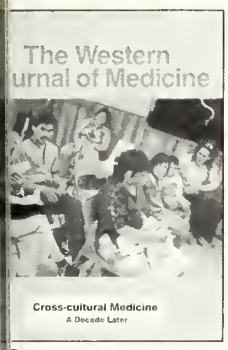

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- GYPSIES AND HEALTH CARE *Anne Sutherland*
- EMOTIONAL AND PHYSICAL SENSITIVITY IN IRANIAN CULTURE *Karen L. Pliskin*
- AFGHAN REFUGEES IN CALIFORNIA—HEALTH ISSUES *Juliene G. Lipson and Patricia A. Omidian*
- THE IMPACT OF ETHNICITY ON THE DECISION TO WITHDRAW LIFE SUPPORT *Jill M. Klessig*
- TRANSLATION IS NOT ENOUGH *Linda Haffner*
- THIS, THAT, AND THE OTHER—A CASE STUDY OF MANAGING ILLNESS IN A FIRST GENERATION KOREAN-AMERICAN FAMILY *Soo-Young Chin*

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- PACIFIC ISLANDERS—MIGRATION AND HEALTH *Judith Fitzpatrick-Nietschmann*
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- CULTURAL VARIATION—NUTRITIONAL AND CLINICAL IMPLICATIONS *Nelson Freimer, Dean Echenberg, and Norman Kretchmer*
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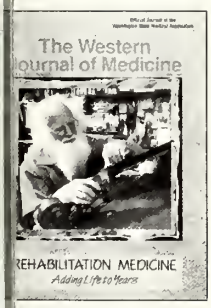

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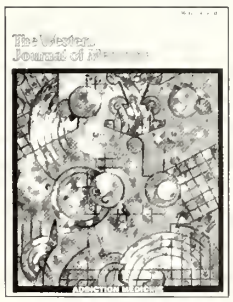

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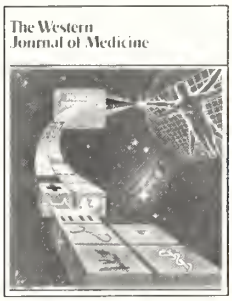

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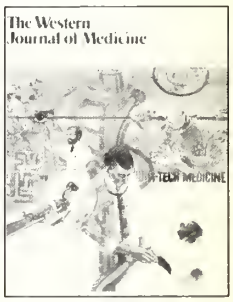

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SAMUEL F. CIRICILLO, MD, and PHILIP R. WEINSTEIN, MD
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JAMES B. REULER, MD, and JAY POORMAN, MD
From the Medical Service, Veterans Affairs Medical Center, and the Department of Medicine, Oregon Health Sciences University School of Medicine, Portland.

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NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

In hypertension or angina therapy

CONSIDER THE CARDIOVASCULAR ENVIRONMENT

INTRODUCING ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

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Please see brief summary of prescribing information on last page of this advertisement.

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

Hypertension or angina control

THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

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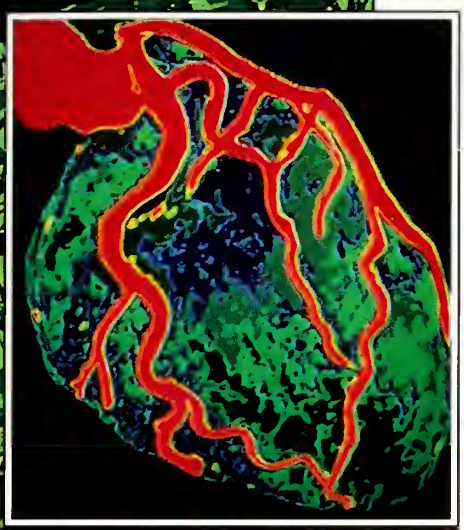
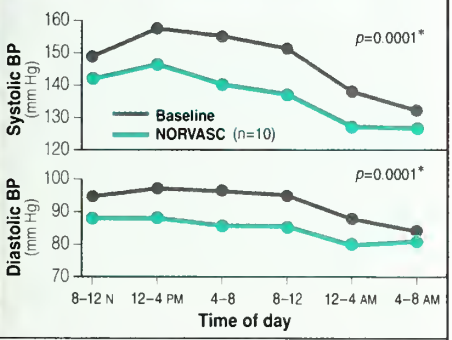


Digital subtraction angiography of the heart

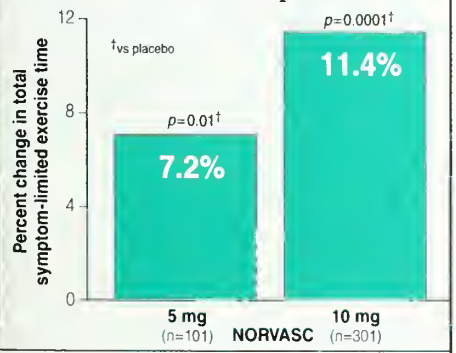
Mean blood pressure (BP) over 24 hours (week 4 data)[1]



Results of a double-blind, randomized, parallel, placebo-controlled study of NORVASC on ambulatory BP in 15 evaluable hypertensive patients (diastolic BP range: 95 to 114 mm Hg). 10 on NORVASC, 5 on placebo. A 4-week, single-blind, placebo run-in period was followed by 4 weeks of double-blind therapy. Ambulatory BP was measured for 24 hours at the end of the placebo run-in phase and after double-blind therapy. (Data on file.[1])

*Average of mean BP values over 24 hours at week 4 versus baseline averages

Change in symptom-limited exercise time measured 24 hours postdose[1]



Data from eight placebo-controlled, double-blind, randomized studies of the effect of NORVASC on symptom-limited exercise time. All studies included a 2-week, single-blind, placebo run-in period. The eight studies included five monotherapy trials and three add-on therapy trials. Treatment ranged from 4 to 6 weeks. Placebo group (n=297) had a 2.1% increase in symptom-limited exercise time. Exercise time at baseline: placebo, 480 sec; 5 mg, 523 sec; 10 mg, 493 sec. (Data on file.[1])

New for Hypertension or Angina

NORVASC, a calcium channel blocker (CCB), provides effective yet gentle 24-hour control with intrinsic once-daily dosing[1]

EFFICACY

Effective for mild, moderate, and severe hypertension[1]

- Over 80% of patients responding to NORVASC are controlled on 5 mg[1]
- 92% of patients remained on NORVASC for 1 year in a long-term study[2]

Effective for chronic stable and vasospastic angina[1]

- 24-hour angina protection, including the morning hours[1]
- Effective alone or in combination with beta blockers

SAFETY

Gradual onset of action and minimal adverse effects

- No clinically significant effects on heart rate[1] or cardiac conduction[1]; no negative inotropic effects at clinical doses in hemodynamic studies,[‡] even when administered with beta blockers to humans[1]
- Has been used safely in patients with concomitant diseases
  —Chronic obstructive pulmonary disease, well-compensated Class II-III congestive heart failure (CHF),[§] peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles[1]
- Neutral effect on lipids[1]; no impairment of normal renal function[1]
- No drug interaction with digoxin, warfarin, or cimetidine[1]

Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects[1]

- The most common side effects are headache and edema

‡Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.
§Therapy should be initiated with caution. See PRECAUTIONS section of brief summary.

NEW, ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

HYPERTENSION OR ANGINA CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

SAFETY

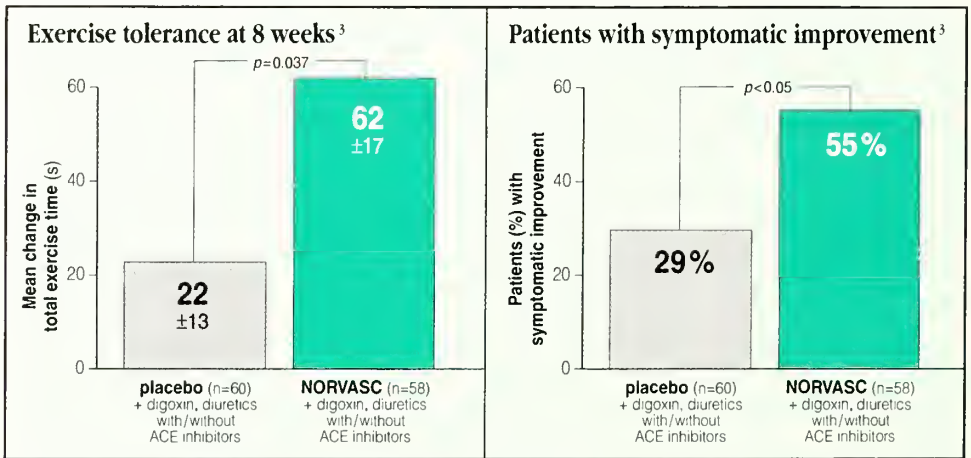
Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects[1]

Dose-related side effects

Adverse event	NORVASC (%) 5 mg (n=296)	NORVASC (%) 10 mg (n=268)	placebo (%) (n=520)
Edema	3.0	10.8	0.6
Dizziness	3.4	3.4	1.5
Flushing	1.4	2.6	0.0
Palpitation	1.4	4.5	0.6

Caution should be exercised when using CCBs in any patient with heart failure

— In a double-blind study of 118 patients with mild to moderate CHF, NORVASC did not adversely affect cardiac function in patients with impaired LV function (LV ejection fraction < 40%)[3]



Results of a randomized, multicenter, double-blind, placebo-controlled trial of NORVASC in 118 patients with well-compensated CHF. All had New York Heart Association (NYHA) Class II or III symptoms, with LV ejection fractions < 40% (averaging 25%[1]). NORVASC dose: 10 mg qd. Patients were already on therapy with digoxin and diuretics, and 80 patients were also taking angiotensin-converting enzyme (ACE) inhibitors. (Adapted from Packer M et al, *J Am Coll Cardiol*, 1991[3]) CHF patients did not have active angina or hypertension at the time of the study. Baseline exercise values: NORVASC, 570 sec; placebo, 613 sec. Symptomatology rating based on investigators' subjective global assessment. (Data on file[1])

— In this study, NORVASC did not increase plasma norepinephrine levels, and ejection fraction did not change[3]

— Studies in patients with NYHA Class IV heart failure have not been performed

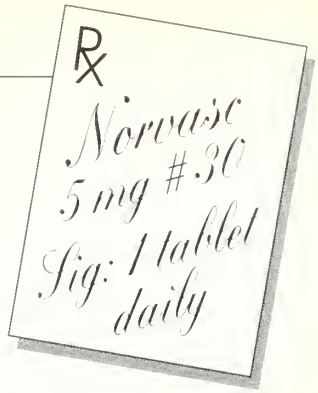
— NORVASC therapy, despite these findings, should be used with caution in patients with heart failure until safety in these patients can be confirmed with additional clinical experience

Please see brief summary of prescribing information on last page of this advertisement.

DOSING

Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension
  - —In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily
- Titration can proceed to 10 mg
  - —Most angina patients will require 10 mg
- Can be taken with or without food



NEW, ONCE-DAILY NORVASC® (amlodipine besylate)

5-mg and 10-mg tablets

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

References:
1. Data on file. Pfizer Inc, New York, NY. **2.** The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med.* 1991;151:1413-1423. **3.** Packer M, Nicod P, Khandheria BR, et al. Randomized, multicenter, double-blind, placebo-controlled evaluation of amlodipine in patients with mild-to-moderate heart failure. *J Am Coll Cardiol.* 1991;17:274A. Abstract.

Brief Summary
NORVASC® (amlodipine besylate) Tablets
For Oral Use

CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in NYHA Class III-IV heart failure patients have shown that NORVASC did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal, any such withdrawal should be by gradual reduction of the dose of the beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life ($t\frac{1}{2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo), dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo), flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo), and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo), fatigue (4.5%, compared with 2.8% placebo), nausea (2.9%, compared with 1.9% placebo), abdominal pain (1.6%, compared with 0.3% placebo), and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women), flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women), palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women), and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension; **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting; **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** thirst; **hemopoietic:** purpura.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized, another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive, the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg.
**These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

More detailed professional information available on request.
Revised August 1992

Pfizer Labs

(Continued from Page 118)

March 15-19—**Emergency Medicine Symposia II.** UCSD at La Jolla. Mon-Fri. Contact: UCSD.

March 24-28—**Winter Wilderness Medicine: 1993.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (800) 888-5632.

March 31-April 3—**Advances in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Wed-Sat. 19 hrs. Contact: UCSF.

May 10-14—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 12-16—**Wound Management Workshop for Primary Care Physicians.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $475. Contact: UCSD.

June 21-25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

ENDOCRINOLOGY/METABOLISM

February 19-20—**New Horizons in Diabetes Therapy.** Scripps Clinic and Research Foundation at Scripps Memorial Hospital, La Jolla. Fri-Sat. $175. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 5—**19th Annual Diabetes Symposium.** UCD at Sheraton Sunrise, Rancho Cordova. Fri. 6 hrs. Contact: UCD.

March 10-11—**Advances in Endocrinology and Metabolism.** UCSF at Ritz-Carlton Hotel, San Francisco. Wed-Thurs. 14 hrs. $295. Contact: UCSF.

March 11-13—**Treating the Disease of Obesity: Dilemmas and Decisions for the Health Care Professional.** UCLA at Miramar Sheraton Hotel, Santa Monica. Thurs-Sat. 17 hrs. $262. Contact: UCLA Extension.

March 12-13—**Diabetes Update.** UCSF at Ritz-Carlton Hotel, San Francisco. Fri-Sat. 11 hrs. $245. Contact: UCSF.

FAMILY PRACTICE/PRIMARY CARE

February 20—**Cardiology for the Primary Care Physician.** UCD at Cancer Center Auditorium. Sat. 6 hrs. $95. Contact: UCD.

March 24-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Fri. 15.5 hrs. $300. Contact: UCSF, Department of Family and Community Medicine.

April 10-17—**Primary Care Medicine: Update 1993.** UCSF at Maui Inter-Continental Hotel, Wailea, Hawaii. 1 week. 20 hrs. $545. Contact: UCSF.

April 17—**Ophthalmology for Primary Care.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

April 22-24—**Rheumatology for Primary Care Physicians.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 14 hrs. Contact: UCSF.

April 22-25—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 23-25—**Family Practice: Today and Tomorrow.** UCSD at San Diego Hilton. Fri-Sun. 14 hrs. $150. Contact: UCSD.

July 5-8—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

HEMATOLOGY

February 14-17—**Clinical Hematology and Oncology: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Sun-Wed. 18 hrs. $385. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

March 11-13—**Recent Advances in Autologous Hematopoietic Stem Cell Transplantation.** UCSD at San Diego Hilton Beach and Tennis Resort. Thurs-Sat. 16 hrs. $300. Contact: UCSD.

March 17-20—**5th International Symposium on Blood Substitutes.** UCSD at Sheraton Harbor Island. Wed-Sat. Contact: UCSD.

April 25-28—**10th Scientific Meeting of the Inter-American Society of Hypertension.** UCSD at Sheraton-Grande Torrey Pines. Sun-Wed. 39 hrs. $300. Contact: UCSD.

April 28—**World Hypertension League Symposium.** UCSD at Sheraton-Grande Torrey Pines. Wed. 4 hrs. Contact: UCSD.

INFECTIOUS DISEASES

March 16-18—**Planning and Evaluation HIV Programs.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 23-25—**STD/HIV for Outreach Workers.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 30-31—**HIV Update.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Wed. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 2-3—**Fighting for Their Lives: You Can Make a Difference—HIV Update.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 9 hrs. $130. Contact: UCD.

April 12-24—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1¾ wks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 28-30—**Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. Contact: UCSF.

May 24-29—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Sat. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

INTERNAL MEDICINE

February 20-25—**Topics and Advances in Internal Medicine.** UCSD at Hyatt Regency, San Diego. Sun-Thurs. 45 hrs. $595. Contact: UCSD.

February 26-27—**Advances in Vascular Diseases.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

March 1-5—**31st Annual Critical Care Medicine.** USC at Caesar's Palace, Las Vegas, Nevada. Mon-Fri. 25 hrs. $595-$680. Contact: USC.

March 19-25—**Internal Medicine 1993: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Tues. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5-8—**Controversies and Agreements in Internal Medicine.** Group Health Cooperative at Intercontinental Hotel, Maui, Hawaii. Mon-Thurs. 19 hrs. $425. Contact: GHC, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

NEUROLOGY

February 27—**Evaluation and Management of the Dizzy Patient.** UCLA at Neuropsychiatric Institute Auditorium. Sat. 5.5 hrs. $65. Contact: UCLA Extension.

May 14-16—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sun. 12 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

June 12-14—**Pharmacological Approaches to the Treatment of Chronic Pain: Current Concepts and Critical Issues.** UCSF at Doubletree Fisherman's Wharf, Monterey. Sat-Mon. Contact: UCSF.

OB/GYN

February 17-19—**Contemporary Obstetrical and Transvaginal Ultrasound.** UCSD. Wed-Fri. Contact: UCSD.

March 18-20—**Prevention of Prematurity and Neonatal Mortality.** UCSD at Loew's Coronado. Thurs-Sat. 13 hrs. $370. Contact: UCSD.

April 14-18—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Susan Butler, PCFS, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (310) 947-7068.

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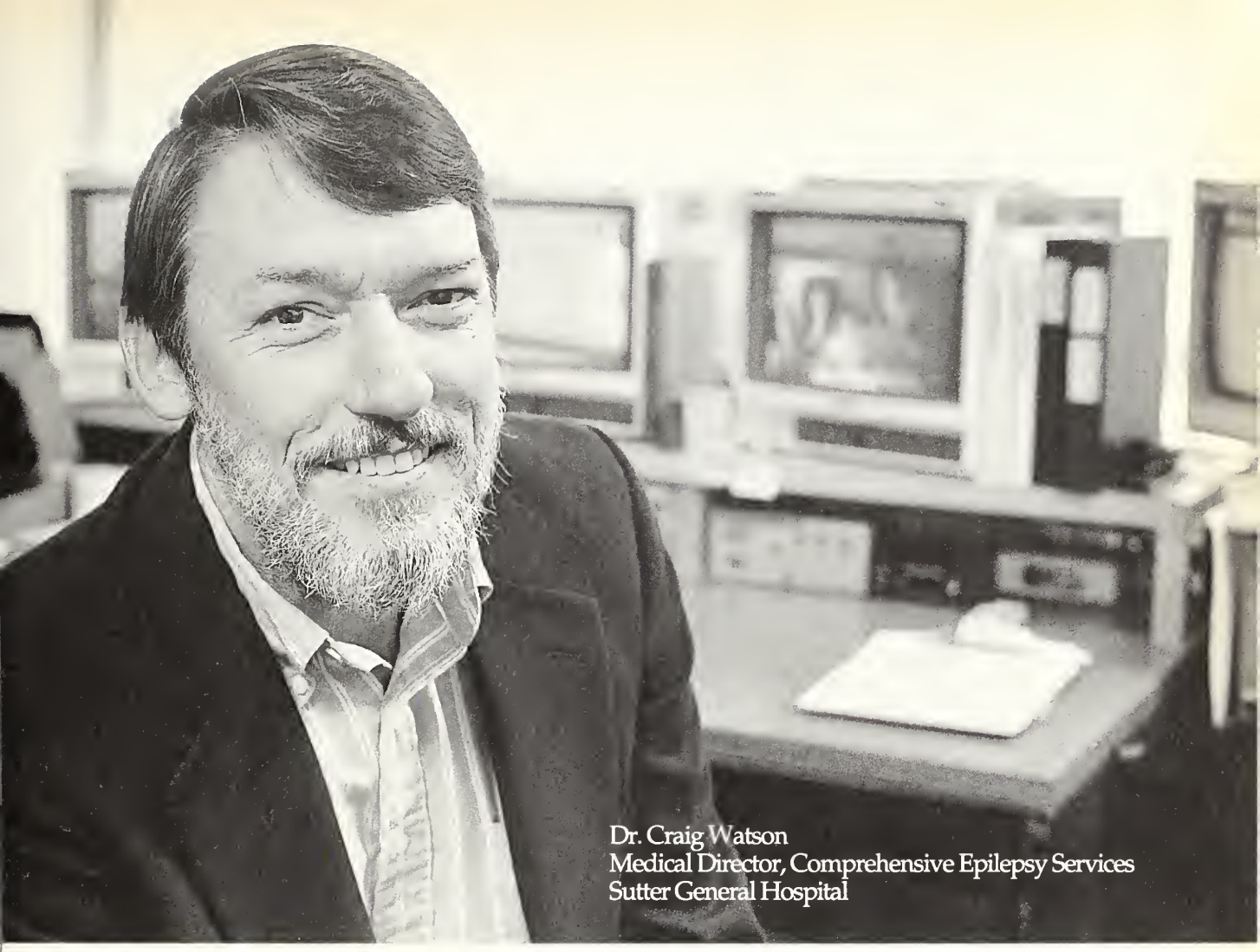

Dr. Craig Watson
Medical Director, Comprehensive Epilepsy Services
Sutter General Hospital

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For more about services or patient transfers, call Sutter Neuroscience Center at Sutter General Hospital in Sacramento, (916) 455-4323.

Sutter Neuroscience Center

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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Manuscript Information

Manuscripts should be sent to the Editor, Linda Hawes Clever, MD, *The Western Journal of Medicine*, 221 Main Street, San Francisco, California 94105. Manuscripts must be original, not previously published, and not under consideration by another publication. If preliminary data were included in another presentation or publication, that should be noted in the cover letter and a copy of that publication should be included.

Manuscripts should not exceed 3,000 words (15 double-spaced pages). Case Reports, Alerts, and Notices should not exceed 1,500 words. Lessons From the Practice should not exceed 1,000 words.

Manuscripts, except for Case Reports, Epitomes, and Lessons From the Practice, should include an abstract of no more than 200 words summarizing the article. Abstracts should include a description of the purpose, design, patients, results, and conclusions.

Letters to the Editor must be double-spaced and will be published at the discretion of the Editors. They may be edited for style and brevity. Those of a scientific nature may be subject to peer review. They should be no more than 500 words in length. Authors will be sent galley proofs before publication.

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Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456
2. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)
4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983
7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

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This material should not be included in the reference list but should be given in parentheses in the body of the text, listing the person's name, highest academic degrees, and professional affiliation, whether the communication was oral or written, and the date (month and year).

Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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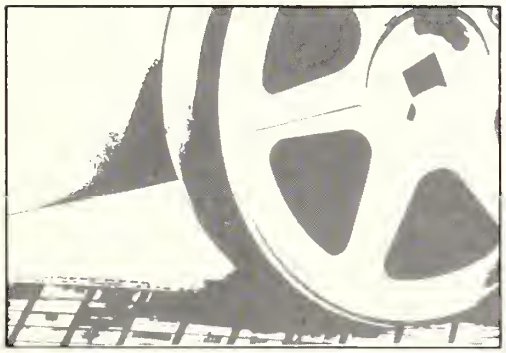

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Lower Respiratory Tract Infections caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Otitis Media caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β-lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibiotic drug effective against *C. difficile*.

Precautions: General. While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

Dosage and Administration: The *Augmentin* 250 mg tablet and the 250 mg chewable tablet do *not* contain the same amount of clavulanic acid (as the potassium salt). The *Augmentin* 250 mg tablet contains 125 mg of clavulanic acid, whereas the 250 mg chewable tablet contains 62.5 mg of clavulanic acid. Therefore, the *Augmentin* 250 mg tablet and the 250 mg chewable tablet should *not* be substituted for each other, as they are not interchangeable.

Since both the *Augmentin* 250 mg and 500 mg tablets contain the same amount of clavulanic acid (125 mg, as the potassium salt), two *Augmentin* 250 mg tablets are not equivalent to one *Augmentin* 500 mg tablet. Therefore, two *Augmentin* 250 mg tablets should not be substituted for one *Augmentin* 500 mg tablet for treatment of more severe infections.

Dosage: Adults: The usual adult dose is one *Augmentin* 250 mg tablet every eight hours. For more severe infections and infections of the respiratory tract, the dose should be one *Augmentin* 500 mg tablet every eight hours.

Children: The usual dose is 20 mg/kg/day, based on amoxicillin component, in divided doses every eight hours. For otitis media, sinusitis and lower respiratory tract infections, the dose should be 40 mg/kg/day, based on the amoxicillin component, in divided doses every eight hours. Severe infections should be treated with the higher recommended dose.

Children weighing 40 kg and more should be dosed according to the adult recommendations.

BRS AG L4

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When you suspect ß-lactamase-resistant bronchitis and pneumonia*

The bugs stop here

AUGMENTIN®

amoxicillin/clavulanate potassium

Augmentin®: 8 years of undiminished efficacy[1]

- Active against important pathogens– *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*†
- Actively destroys ß-lactamase resistance[2,3]
- Clinical response rate of 98% in bronchitis and pneumonia[1]

* For susceptible strains of indicated organisms.
† *In vitro* activity does not necessarily imply *in vivo* efficacy

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on the previous page.

References: 1. Data on file, SmithKline Beecham Pharmaceuticals. **2.** Brown R, Pinkerton R, Tuttle M Respiratory infections in smokers. *Am Fam Physician* 1987;36:133-140. **3.** Neu HC Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79 (suppl 5B):2-12.

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Articles

Immediate Health Effects of an Urban Wildfire

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To document the immediate health effects of the urban wildfire that swept through parts of Alameda County, California, on October 20 and 21, 1991, we conducted a retrospective review of emergency department and coroner's records. Nine hospitals (6 local and 3 outlying) were surveyed for the week beginning October 20, 1991. Coroner's reports were reviewed for 25 identified fire-related deaths. A total of 241 fire-related emergency encounters, including 44 inpatient admissions, were recorded for 227 persons. Nearly a fourth of emergency department patients were seen for work-related injuries, more than half of which occurred among professional firefighters. Smoke-related disorders constituted more than half of all emergency department cases; of these, 61% had documented bronchospasm. Major trauma and burns contributed 1% and 4% of principal diagnoses, respectively; these were exceeded in number by corneal abrasions (13%), other medical problems (8%), and minor trauma (7%), among other diagnoses. All coroner's cases involved extensive burns, many with documented smoke inhalation injury. While the Oakland-Berkeley fire storm resulted in a high case-fatality ratio among major burn cases (25/31), those who survived the initial fire storm did well clinically. Among emergency department patients, medical (particularly smoke-related) disorders outnumbered traumatic presentations by a ratio of more than 2 to 1.

(Shusterman D, Kaplan JZ, Canabarro C: Immediate health effects of an urban wildfire. West J Med 1993 Feb; 158:133-138)

On Sunday, October 20, 1991, a grass fire in the Oakland-Berkeley hills of northern California that was believed to have been extinguished on the previous day flared into one of the largest urban fires in US history. The fire was fueled by dry vegetation resulting from five consecutive years of drought and was fanned by unusually hot and dry northeasterly winds. Over the course of the next two days, more than 1,600 acres of hilly residential land burned, destroying or damaging approximately 3,800 dwelling units, killing 23 civilians and 2 public safety workers, and sending scores of persons to area emergency departments.[1] A smoke and ash plume rose to between 1,800 and 5,000 ft altitude and extended over at least 30 miles (Bay Area Air Quality Management District, oral communication, October 1991).

More than 1,500 firefighting personnel from 244 local, 4 military, and 2 state agencies fought the blaze over a three-day period.[1] Local police and public safety officers evacuated residents and controlled traffic and crowds. Emergency medical services were provided by at least nine area hospitals. In this article we summarize the immediate health effects of the fire—through the first week after the fire—as ascertained from emergency department records and coroner's reports.

Methods

Cases were researched at six local (Oakland and Berkeley) and three outlying hospitals. The latter were selected because of either their inpatient burn units or their regional trauma center status (Table 1). Study personnel reviewed emergency department logs and medical records for patients registered between 11 AM on Sunday, October 20, and 11:59 PM on Saturday, October 26. Our initial case search was aided by lists of fire-related cases compiled by emergency department administrators during the first two days of the fire. In addition, several diagnostic types were selected for review from the emergency department logs, including all trauma, burns, chest pain, respiratory disorders, smoke inhalation, conjunctivitis, corneal abrasions, mental health problems, and problems placing chronically ill patients. Criteria for inclusion in the study were treatment in an emergency department during the described time frame plus documentation in the medical record that, in the opinion of the treating physician, the fire was a causal, precipitating, or exacerbating factor for the presenting complaint. The locations of the fire and of the hospitals surveyed are shown in Figure 1.

We reviewed records using a standardized abstraction form. Data abstracted included demographics (age, sex,

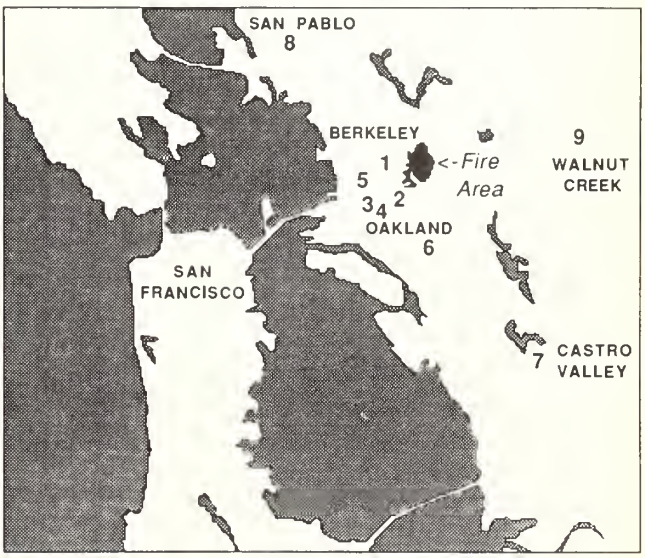

Figure 1.—General fire area and locations of hospitals surveyed are shown on this map of the Bay Area. (See Table 1 for key to hospitals.)

From the California Office of Environmental Health Hazard Assessment, Air Pollution Epidemiology Unit (Dr Shusterman); the Alta Bates Hospital Burn Center (Dr Kaplan); and the California Public Health Foundation (Dr Canabarro), Berkeley, California.

Reprint requests to Dennis Shusterman, MD, MPH, Office of Environmental Health Hazard Assessment, Air Pollution Epidemiology Unit, 2151 Berkeley Way, Annex 11, Berkeley, CA 94704.

TABLE 1.—*Characteristics of Hospitals Surveyed, With Number and Types of Initial Visits*

No.	Hospital	City in California	Type*	Licensed Beds, No.	Relevant Areas of Specialty	Total Initial Visits, No.	Emergency Department Only, No.	Admissions and Transfers, No.
1	Alta Bates-Herrick†	Berkeley	1	469	Inpatient burn unit	61	51	10
2	Kaiser Foundation	Oakland	2	300	--	46	39	7
3	Merritt-Peralta	Oakland	1	260	--	36	27	9
4	Providence	Oakland	1	238	--	35	30	5
5	Oakland Children's	Oakland	1	205	Pediatric trauma center	19	13	6
6	Highland General†	Oakland	3	300	Regional trauma center	16	12	4
7	Eden†	Castro Valley	1	238	Regional trauma center, inpatient burn unit	9	8	1
8	Brookside†	San Pablo	4	246	Inpatient burn unit	3	3	0
9	John Muir	Walnut Creek	1	317	Regional trauma center	2	2	0
	Total					227	185	42

*Hospital types: 1 = private, nonprofit; 2 = health maintenance organization; 3 = public, governmental; 4 = public, district.

†These hospitals are participants in an ongoing study of smoke inhalation victims sponsored by the Federal Emergency Management Agency-US Fire Administration and the International Association of Fire Fighters-Burn Foundation.

race, and residence location); date, time, and mode of arrival in emergency department; type of visit (emergency department only, inpatient admission, or transfer); work-relatedness of injury (with occupation and employer if appropriate); chief complaint, discharge diagnosis, and type and severity of injuries and medical complaints. For persons identified from medical records as exposed to smoke, the initial carboxyhemoglobin level was recorded, if available. For fatalities, cause and circumstances of death, description of injuries, and results of toxicologic analyses were obtained from the Alameda County Coroner's Office. Data were entered and analyzed using Epi-Info, Version 5.01b (Centers for Disease Control, Atlanta, Georgia).

Hospital cases were classified for study purposes based on the principal discharge diagnosis (for those admitted as inpatients) or the first condition listed in the diagnosis section of the emergency department record (for those treated as outpatients), except when an obvious competing diagnosis of greater severity influenced the level of emergency care. Because many of the participating hospitals did not code outpatient emergency department records according to the system recommended in the *International Classification of Diseases*[2] and because coding ambiguities may arise when there is an imputed environmental agent, such as smoke, cases were categorized according to the functional scheme described here.

Trauma

Major trauma was defined as life-threatening or incapacitating trauma involving the central nervous system, thorax, or abdomen or orthopedic trauma endangering neurovascular structures or causing risk of exsanguination. Minor trauma included uncomplicated lacerations, puncture wounds, contusions, sprains, strains, abrasions, and conjunctival foreign bodies. Corneal abrasions were defined by abnormal fluorescein staining of the cornea. Fractures without secondary complications were distinguished from major trauma. Burns were subdivided into inpatient and outpatient categories based on severity.

Smoke-Related Disorders

Irritative reactions to smoke included smoke-related headache, conjunctivitis, nasopharyngitis, sinusitis, tracheitis, acute bronchitis without wheezing, and nonspecific

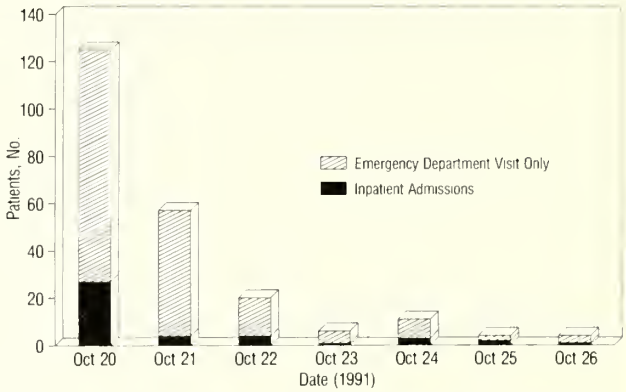

Figure 2.—The graph correlates initial emergency department visits and inpatient admissions, by day, for the period October 20 to 26, 1991.

smoke inhalation without wheezing. Bronchospastic reactions to smoke included acute exacerbations of asthma and chronic obstructive pulmonary disease, asthmatic bronchitis, bronchospasm, and reactive airways disease, in each case with the auscultatory finding of wheezing documented in the medical record.

Other Medical, Psychiatric, and Social Service Problems

Medication refills was a category limited to patients without acute symptoms. Other medical problems included chest pain, nontraumatic chest wall pain, and gastrointestinal, skin, and other nontraumatic disorders. Mental health problems, including acute exacerbations of underlying psychiatric disorders and acute situational stress or grief reactions, were also seen. The final category was evacuation or placement difficulties, referring to displaced persons with chronic medical conditions rendering referral to shelters inappropriate.

Results

Emergency Department Visits and Hospital Admissions

A total of 241 emergency department visits were documented for 227 persons, with 44 inpatient admissions. Of the admissions, 42 occurred at the time of the initial visit and 2 on follow-up evaluation. The number of initial emergency

department visits and inpatient admissions by hospital are shown in Table 1, and their timing is shown in Figure 2. The numbers follow a roughly inverse relationship to the distance of each hospital from the fire zone.

The demographic characteristics of patients seen in local emergency departments and of coroner's cases are shown in Table 2. Overall, there was a predominance of male to female patients, although this excess was largely limited to those injured in the course of employment. Residents of Oakland and Berkeley together contributed 72% of emergency department visits. Table 3 gives the occupational status of patients. Almost 25% of all cases were work related; among these, roughly half were among professional firefighters, and the rest were nearly evenly split between volunteer firefighters and people of other occupations.

TABLE 2.—*Characteristics of Emergency Department Patients and Direct Fire Fatalities*

Characteristic	*Patients (n=227)*	*Fire Fatalities (n=25)**
Age		
Range	3 mo-97 yr	18-85 yr
Mean	38.7 yr	54.6 yr
Sex	*No. Male/Female*	
All patients	140/87	11/14
Patients with non-work-related conditions	90/83	9/14
Patients with work-related conditions	50/4	2/0
City of Residence	*No. (%)*	*No. (%)*
Oakland	120 (53)	17 (68)
Berkeley	44 (19)	5 (20)
Other	63 (28)	3 (12)
Total	227 (100)	25 (100)

*An additional indirect fire-related fatality is documented in the text.

TABLE 3.—*Occupational Status of Emergency Department Patients*

Work Status of Admitting Condition	*Patients, No. (%)*	*Patients, No. (%)*	*Patients, No. (%)*
Not work related	173 (76)	--	--
Work related	54 (24)	--	--
Firefighters	--	40 (74)	--
Professional	--	--	28 (70)
Volunteer	--	--	12 (30)
Police officers	--	4 (7)	--
Other	--	10 (19)	--
Total	227 (100)	54 (100)	40 (100)

The diagnoses of patients treated in emergency facilities are categorized in Table 4. The leading diagnostic categories were bronchospastic reactions to smoke (31%), irritative reactions to smoke (20%), corneal abrasions (13%), other medical problems (8%), and minor trauma (7%). It is interesting to note that almost half of the corneal abrasions and more than 25% of the irritative reactions to smoke occurred among professional and volunteer firefighters, who together constituted only 18% of all patients seen. On the other hand, no firefighters were seen in the emergency department with a principal diagnosis of burns, and only two were seen with bronchospastic reactions to smoke.

The Oakland Fire Department (the employer with the largest number of fire-related injuries) contracts with an outpatient physician group to treat nonemergency work-related injuries; such outpatient care was available beginning with the second day of the fire. It is therefore likely that our case search significantly underestimated the number of minor injuries among local professional firefighters (Capt. William Salters, oral communication, November 1991). Similarly, many persons injured nonoccupationally may have sought care in nonemergency outpatient settings and thus would not be reported here.

Major Trauma

Three cases were ultimately classified as major trauma; one patient was treated at the regional trauma center closest to the fire area (hospital 6), one at the pediatric trauma center (hospital 5), and one at a hospital not designated as a trauma center (hospital 2). Another three patients were treated either as trauma team cases or trauma consultations at hospital 6; after examining discharge diagnoses, two of these cases were classified here as minor trauma and the last as an inpatient

TABLE 4.—*Principal Diagnoses of Patients Seen in Emergency Settings, With Occupational Status*

Diagnostic Category	*Number of Cases: Emergency Department Only*	*Admissions*	*Total (%)*	*Firefighters (Professional and Volunteer), No.*	*Other Occupations, No.*	*Non-occupational, No.*
Bronchospastic reactions to smoke	54	17	71 (31)	2	1	68
Irritative reactions to smoke	42	4	46 (20)	12	3	31
Corneal abrasions	29	0	29 (13)	13	4	12
Other medical problems	17	2	19 (8)	4	2	13
Minor trauma	14	1	15 (7)	6	3	6
Evacuation or placement	4	9	13 (6)	--	--	13
Mental health problems	11	0	11 (5)	1	0	10
Fractures (simple)	5	3	8 (4)	2	0	6
Burns (inpatient)	0	6	6 (3)	0	0	6
Medication refill	4	0	4 (2)	--	--	4
Major trauma (other than burns)	1*	2	3 (1)	0	1	2
Burns (outpatient)	2	0	2 (1)	0	0	2
Total	183	44†	227 (100)‡	40	14	173

*One patient was unable to be resuscitated in the emergency department. †Includes 2 admissions from follow-up (non-initial) visits. ‡Percentages may not total correctly because of rounding.

burn. A total of 54 ambulance transports were documented from hospital records.

Burns

Seven people had minor burns not requiring admission, with severity ranging from punctate blisters on the eyelids to second-degree burns over 5% of the upper extremities. Burns were the principal diagnosis for only two outpatients. Only one professional and one volunteer firefighter were noted to have burns, in neither case as the principal diagnosis.

Six patients with burns were treated in hospital. The range of body surface area involvement among inpatients was 12% to 43% (mean 24%). The burns were predominantly second degree in depth, although two inpatients had third-degree burns of minor extent and a third had widespread, deep second-degree burns. One patient had a serious inhalation injury with transient myoglobinuric renal failure.

Qualitatively, some unusual burn patterns were noted. Among the inpatients, burns were usually patchy in distribution, reflecting the fact that flaming debris had struck the patients. In addition, the finding of confluent areas of deep second-degree burns with lines of burn demarcation at the edges of clothing and intact body hair suggested that radiant (infrared) heat may have conveyed a substantial part of the thermal injury. Cinders were apparently responsible for the punctate distribution of burns in some outpatients.

Smoke-Related Disorders

Overall, bronchospastic and irritative reactions to smoke constituted more than half of the emergency department visits related to the fire, with bronchospastic reactions alone constituting nearly a third of all cases. Among the 71 patients with bronchospasm related to smoke, 16 were admitted as inpatients on their first day of treatment, 1 was admitted on a follow-up visit, and 4 had several outpatient visits during the week after the fire. Approximately two thirds of these patients (n = 47; mean age 24 years) had a history of asthma documented on the chart, and another 11% (n = 8; mean age 66 years) had a history of chronic obstructive pulmonary disease. The remaining 23% with bronchospasm and no history of asthma or chronic obstructive pulmonary disease were intermediate in age (n = 16; mean age 33 years). At the single pediatric hospital in the study area, bronchospastic reactions to smoke constituted nearly 85% of fire-related visits and all of the inpatient admissions, the highest proportion among any of the study hospitals. Bronchospastic reactions to smoke led to most of the inpatient admissions after the first day of the fire and the only admissions after day 2 following the fire.

The spectrum of nonbronchospastic irritative effects from smoke ranged from mild conjunctivitis to tracheobronchitis. Of the 46 patients in this diagnostic group, 4 were admitted as inpatients, 3 with a diagnosis of smoke inhalation and 1 with a smoke-related exacerbation of preexisting fibrotic lung disease; among the patients with smoke inhalation were two professional firefighters. Only one of the four inpatients had acute abnormalities on the admission chest radiograph. The average carboxyhemoglobin level among the 3 inpatient smoke inhalation cases was 0.054 (5.4%), compared with 0.033 (3.3%) among the 17 outpatients with irritative reactions to smoke who were sampled. Some of the patients in this category may have had bronchospasm without wheezing. Conditions such as "cough-equivalent asthma," however, could not be detected in our retrospective study because the participating emergency departments do not administer pulmonary function tests on a consistent basis.

Other Medical and Mental Health Problems

Among the 19 cases classified with other medical problems were the following principal diagnoses, in order of descending frequency: suspected anginal symptoms, chest pain of unknown cause, poison oak (rhus) dermatitis, nontraumatic chest wall pain, gastroenteritis (possibly from donated prepared food), dehydration, esophageal spasm, dyspepsia, peptic ulcer disease, and loss of control of diabetes mellitus. Most of the 11 mental health visits were related to situational stress.

Evacuation or Placement Difficulties

The average age of patients evaluated for placement (n = 13) was 87 years, with a range of 71 to 97 years. Documented preexisting debilitating medical conditions in this group included stable chronic obstructive pulmonary disease, dementia, stroke, and congestive heart failure. Nine of these patients were admitted, including two who were transferred to skilled nursing facilities. One hospital opened up a ward for several days to accommodate chronically ill and elderly patients displaced by the fire.

Carboxyhemoglobin Levels

Carboxyhemoglobin (COHb) levels were determined for 43 people (11 professional firefighters, 5 volunteer firefighters, and 27 civilians) on arrival at the emergency department. All hospitals determined COHb levels by differential

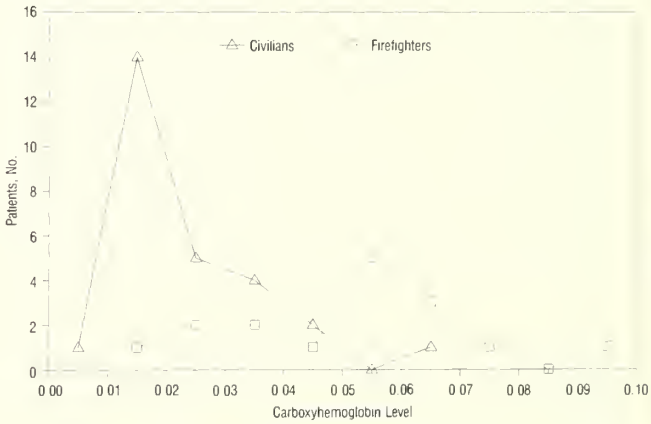

Figure 3.—Measurements of carboxyhemoglobin levels were obtained on 27 civilians and 16 firefighters (11 professionals and 5 volunteers).

spectrophotometry, although the specific manufacturer and model of instruments varied from hospital to hospital. The range of COHb values was from 0.000 to 0.091 (0.0% to 9.1%), with a mean of 0.033 (3.3%). The distributions of COHb values for firefighters and civilians are shown in Figure 3; COHb levels among the 16 professional and volunteer firefighters averaged 0.051 (5.1%) versus 0.023 (2.3%) among the 27 civilians.

Fatalities

The official coroner's count of fire-related deaths was 25, including 23 civilians and 2 public safety personnel. In contrast to emergency department cases, there was a predominance of female over male fatalities. Those who died were,

on the average, older, reflecting the relatively settled demographics of the remote hillside areas (Table 2). The residential distribution of deaths was roughly similar to that of emergency department cases, with Oakland and Berkeley together being the location of 88% of the deaths. Included in our tally is a traffic death that occurred away from the fire site but that was clearly related to traffic diversion around the fire area.

All coroner's cases involved extensive burns, with or without documented smoke inhalation injury. The coroner's office also noted specific traumatic injuries in some cases. Given the rapidity with which the fire moved, the high temperatures involved, and the consequent destruction of physical evidence, it was impossible for the coroner's office to attribute specific underlying or contributory causes of death or to reconstruct premortem events in most cases.

The forensic toxicology protocol for the County of Alameda Sheriff's Office involves determining COHb, cyanide, and ethanol blood levels for all cases of death by burns or smoke inhalation for which suitable specimens are available (Paul Herrmann, MD, oral communication, December 12, 1991). The COHb levels (n = 16) ranged from 0.02 to 0.51 (2% to 51%), with a mean of 0.14 (14%). Measured cyanide levels (n = 18) ranged from nondetectable (less than 6 μmol per liter [<0.15 μg per ml]) to 60 μmol per liter (1.56 μg per ml), with a mean of 9.8 μmol per liter (0.26 μg per ml). Only 2 of 16 blood specimens had ethanol levels in the detectable range: 4.3 and 34.7 mmol per liter (20 and 160 mg per dl).

Discussion

Trauma

Major trauma (other than burns) was relatively rare, involving motor vehicle accidents in two cases and a fall from a roof in the third. One motor vehicle accident was related to a motorist running a stop sign while fleeing the fire; the victim was on a motorcycle and was wearing a helmet. The other was related to the diversion of traffic on a freeway that traverses the fire area; the victim was an unrestrained passenger. Both of these cases involved head injuries, in one case being fatal. Five of the nine documented fractures involved the lower extremities, and the predominant mechanisms of injury were falling, jumping, and running on uneven ground. The pattern of minor trauma was unremarkable under the circumstances.

Fatalities and Burns

The high case-fatality ratio among major burn patients (25/31) was attributable to the rapid spread of the fire and the impeded escape in many areas; many residents were overtaken by flames as they attempted to flee. On the other hand, those who survived their initial burn injuries did well. Whereas some residents were trapped in their homes, others fell victim to traffic bottlenecks exacerbated by narrow hillside roads. In one stretch of road, for example, 11 people perished. Inspection of the area later revealed that the 13-ft-wide road (half the minimum national standard width) had become obstructed by fleeing vehicles (M. Taylor and B. Wallace, "Charing Cross Bottleneck Was Big Killer," *San Francisco Chronicle*, November 2, 1991, p A14). In addition to area residents, two public safety officers (one firefighter and one police officer) died while attempting to lead civilians to safety.

The burn injuries among survivors were treated roughly equally on an inpatient and outpatient basis. As noted earlier, many of the burns displayed either a patchy quality (related to exposure to flaming debris) or a pattern related to radiant heat. The effectiveness of the "turnout coat" worn by firefighters against both of these hazards was attested to by the virtual absence of burns documented among firefighters.

Smoke-Related Disorders

The intensity and duration of smoke exposure ranged from mild and transient (among residents of surrounding areas) to intense and prolonged (among firefighters and some residents of the fire area). Although obvious risk factors for a bronchospastic response to smoke include antecedent asthma and chronic lung disease, some persons may wheeze for the first time after smoke exposure.[3,4] Reports of bronchospasm among residents some distance from the fire are consistent with published reports on the exacerbation of asthma by particulate air pollution.[5-7] Observations of particulate-triggered asthma have recently been extended to include smoke from forest fires[8] and from an urban warehouse fire (Michael Lipsett, MD, unpublished data, January 1991), with 40% to 60% increases in the number of local emergency department visits for asthma being typical during large fires.

Occupational Health Issues

Urban (structural) firefighters have been noted to be at high risk for smoke inhalation, burns, and falls.[9] Combustion products posing acute inhalation hazards in structural fires include simple asphyxiants (such as carbon dioxide and oxygen-deficient atmospheres), cellular asphyxiants (carbon monoxide and hydrogen cyanide), and various irritants (including nitrogen oxides, particulate matter, organic acids, aldehydes, and chlorine compounds).[10] Wildlands firefighters, by contrast, have been noted to be at lower risk of developing carbon monoxide intoxication than their urban counterparts.[11] Structural firefighters have been shown to be at risk for transient respiratory impairment, with cross-shift changes in forced expiratory volume in 1 second, forced expiratory flow in the midexpiratory phase, and nonspecific bronchial reactivity[12-14]; similar changes have been demonstrated in wildlands firefighters on a cross-seasonal basis.[15]

The Oakland-Berkeley fire showed characteristics of both structural and wildlands fires. Similar to a wildlands fire, little of the firefighting took place in enclosed spaces—hence, the relatively low COHb levels observed in firefighters. At the same time, the prolonged firefighting hours and rugged terrain rendered impractical the respiratory protective gear often used in structural firefighting (the self-contained breathing apparatus). The combination of long and arduous work hours, dehydration, respiratory tract irritation, and low-level carbon monoxide exposure took its toll on many of the firefighters: 30% of firefighter emergency department cases had a principal diagnosis of irritative reaction to smoke, compared with only 18% of civilians. The issue of eye protection was highlighted by the relative prominence of corneal abrasions among firefighter casualties (33% of firefighters versus 7% of civilians).

Carboxyhemoglobin Levels

The observed COHb levels among emergency department patients were relatively low, consistent with the predominantly outdoor exposure conditions. The levels observed here, however, are in the same range as those noted

to shorten the time to angina in a treadmill study of patients with coronary artery disease (0.02 to 0.04, or 2% to 4%)[16] or to increase ventricular ectopy during exercise in a similar group (0.06, or 6%).[17] Among fire deaths, two of the observed COHb levels were potentially life threatening (>0.45) and a third potentially impairing (>0.25). Likewise, the cyanide levels of two who died were in the potentially lethal range (>40 μmol per liter). Although the coroner's office did not speculate on the question of incapacitation before death, it is interesting to view these toxicologic data in light of the recent literature on synergistic toxicity from carbon monoxide and hydrogen cyanide in fire smoke.[18,19]

Mental Health Needs

Probably more than any other health end point, mental health problems are underestimated by examining emergency department visits. The American Red Cross, which operated shelters with volunteer and professional staff, made more than 3,700 contacts for crisis counseling and mental health services (American Red Cross, *East Bay Hills Fire,* DR 590, November 25, 1991). At the University of California at Berkeley, counseling services and the employee assistance program performed active mental health outreach to many of the more than 500 faculty, staff members, and students who were displaced by the fire (Carol Hoffman, LCSW, oral communication, December 1991). The local children's art museum conducted art therapy workshops related to the fire, and a psychiatry grand rounds at a local hospital was devoted to the issue of posttraumatic stress disorder and the fire. Neighborhood support groups, dubbed "Phoenix Societies" after the mythical bird that emerges from its own ashes, sprang up in many fire-ravaged areas; block parties were organized to reestablish neighborhood ties and to honor professional and volunteer firefighters. As of the date of writing, Oakland's metropolitan newspaper still maintains a "fire bulletin board" announcing fire-related meetings and services, including counseling and support groups.

Lessons From the Fire—Prevention

Preventive measures suggested by our examination of the Oakland-Berkeley fire experience can be divided between public safety—fire prevention, evacuation, and emergency response—and public health interventions. In the latter category, the results of our study, like those of others before it,[8] suggest that health advisories should be targeted toward persons with asthma or chronic lung disease, warning them to either stay indoors or vacate areas affected by smoke. Patients taking asthma medications as needed should anticipate the difficulties that smoke will pose and adjust their medication regimens accordingly. Citizens of fire-prone areas should be made aware of the fact that heavy-duty occlusive clothing may provide some protection against radiant heat injuries in escape situations. Firefighters charged with fighting prolonged, smoky, outdoor fires should be encouraged to use protective eyewear and possibly air-purifying (cartridge) respirators when using self-contained breathing apparatus is impracticable.

In the public safety arena, two reports critiquing both advance planning and the emergency response were recently issued by the California Office of Emergency Services and the Federal Emergency Management Agency.[1,20] Among their recommendations were the following:

- Control flammable vegetation near homes;
- Require safer home construction materials (in particular, ban wooden roofs in high-fire-hazard areas);
- Widen streets or prohibit curbside parking in areas with narrow streets, or both;
- Improve communications protocols and equipment for emergency personnel;
- Upgrade and standardize emergency water delivery systems;
- Improve interagency disaster planning; and
- Establish viable evacuation plans for high-fire-risk areas.

Considering the history of major fires in this geographic area (1923, 1946, and 1970), future generations of Oakland-Berkeley hillside dwellers will undoubtedly judge the adequacy of the response to these recommendations.

Acknowledgment

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Black Spots on the Scalps of Schoolchildren

A Recurrent Condition in the Windy West

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During the past 10 years, epidemics of black spots on the scalps of schoolchildren have caused considerable concern in at least 4 communities in the Rocky Mountain states. We describe the clinical presentation of "black spots" in a group of Wyoming elementary school students and the epidemiologic investigation that revealed the cause. Our study included a questionnaire survey of students' parents, examination of students at the affected school and at two other schools, observation of playground activity patterns, and laboratory analysis of specimens taken from affected children and from the school environment. The black material in the scalp spots was chemically identical to flakes of black material found on the playground and tar from the school roof. We concluded that the spots were caused by flakes of windblown tar from the school roof. Previous outbreaks of black spots may have had a similar cause.

(Cobb N, Etzel RA, Hudson R: Black spots on the scalps of schoolchildren—A recurrent condition in the windy West. West J Med 1993 Feb; 158:139-141)

We recently investigated an epidemic of "black spots" on the scalps of elementary school students in a western Wyoming town. During that investigation we learned of at least four outbreaks of a similar condition, in the same region, during the previous ten years. In each situation the condition was apparently benign, but community concern was intense. Concern was increased by the lack of a diagnosis or known cause for the spots. In this article, we present a synopsis of our epidemiologic and laboratory investigation and describe the clinical presentation of "black spots."

Background

In Green River, Wyoming, in 1989, a school nurse noted unusual black spots on the scalps of several children at an elementary school. The spots were presumed to be due to a fungal infection. Local health authorities were notified and a letter was sent to all parents, advising them to keep their children home from school while they had the spots and to have affected children seen by a physician. Many children were examined by physicians; their diagnoses ranged from "dirt" to "presumed tinea." Several children were taken to Salt Lake City for consultation with dermatologists. One diagnosed the spots as "possible macula cerulea," and another wrote that the spots were "inorganic material, from an external source." Only one of the nine schools in the district reported cases.

During the following year, at least half of the 252 students at the affected school had recurrences of the spots. In response to a request from the school district, an investigator from the Wyoming Public Health Laboratory took fungal cultures from the walls and heating system of the school; no predominant organism was isolated. No further action was taken during summer vacation, and parents reported to the school principal that their children had no spots when out of school. Shortly after the start of school in September 1990, the children again began to have black spots. Although the affected children were not ill, the lack of a definitive diagnosis contributed to anxiety in the community. Some parents wanted the school closed while the problem was investigated. School officials requested further assistance from the state. This study was a collaborative investigation by the Wyoming Department of Health and the Centers for Disease Control and Prevention.

Methods

Case Definition

A "black spot" was defined as any black or brown papule greater than 1 mm in diameter that adhered to the scalp but could be removed by scraping with a fingernail or tongue depressor. A case child was defined as any child who had one or more of the characteristic spots on his or her scalp at the time of examination.

Questionnaire

To ascertain risk factors for black spots, a questionnaire was given to all 252 students at the affected school (kindergarten through fifth grade, ages 5 to 12 years) and to a 50% sample of students (first through fifth grades, ages 6 to 12 years) at a second elementary school where the condition had not been reported. The questionnaires were to be filled out at home by the parents and returned to school the following day.

Case Finding

After obtaining parental permission, two of us (N.C. and R.H.) and Gail Poulsen, RN, a Sweetwater County public health nurse, examined the students' heads. All three examiners were present so that the case definition could be applied consistently. A total of 215 students at the index school and

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82 at the second school were examined. We did not examine kindergarten students at any school because they attended school in split sessions, which made scheduling examinations difficult. The following week, to test the hypothesis that the spots were caused by the school roofing material, we examined 80 students at a third elementary school.

Specimens

The index school was inspected thoroughly, inside and out, but only the playground and external features of the eight other schools in Green River were inspected. We collected specimens of the black spots from the heads of three children by gentle scraping with a tongue depressor or metal spatula. To collect windblown debris, we left a washcloth on the playground for 12 hours on a windy day. We collected specimens from the roof of the index school by scraping the exposed tar with a knife.

Laboratory Analysis

The black spots collected from children's heads, the windblown black flakes from the playground, and the school roofing tar were analyzed in the laboratory of the Western Wyoming College Department of Chemistry to determine whether all of these specimens could have come from a common source. Laboratory tests done on the specimens included microscopic examination, gas chromatography, infrared spectrophotometry, and solubility trials.

Experiment

To test the hypothesis that the spots were caused by windblown material, one of us (N.C.) poured about 10 grams of the collected windblown debris onto his hair and wore a hat for 12 hours afterwards. He then rinsed away the excess dirt, and his scalp was examined by the public health nurse.

Results

Clinical Description

Black spots were found on the scalps of children from 5 to 12 years of age. All of the affected children were white, but few dark-skinned children were enrolled in the school. Some children with scalp spots complained of mild pruritus, but most were asymptomatic. The spots were black to brown papules, 1 to 5 mm in diameter (Figure 1). Affected children had from 1 to 20 or more spots at a time. The spots were found only above the hairline on the scalp, not on other exposed skin surfaces. There was no surrounding erythema. A typical spot appeared similar to a nevus or freckle but could be removed by scraping with a tongue depressor. The black material was soft and tenacious, and it had the appearance of tar. The spots could be removed by vigorous washing with regular or keratolytic shampoo.

Differential Diagnosis

Melanocytic nevocellular nevus (mole) has a similar appearance but cannot be so easily removed.

Macula cerulea is a bluish to slate-grey dermal spot caused by subcutaneous bruising from the bites of fleas or lice; it is typically larger (5 to 10 mm), irregular in outline, and most abundant on the chest, abdomen, and thighs. Pediculosis capitis (infestation with head lice) can sometimes be seen as tiny black spots on the scalp; these spots, however, are usually accompanied by lice eggs (nits), which are white and adhere to the hair shafts.

Tinea versicolor typically presents with larger, light brown macules that rarely occur on the scalp. Tinea capitis causes scaling of the skin and hair loss and can be easily diagnosed by a positive potassium hydroxide test for fungal hyphae.

Epidemiologic Investigation

Questionnaires were completed by the parents of 246 (98%) of 252 students at the index school and 99 (79%) of 126 students at the second school. We analyzed only the questionnaires of children we had examined.

At the affected school, 87 (40%) of 215 students examined had one or more scalp spots. Although black spots had not been reported by parents or nurses at the second school, 26 (32%) of 82 students examined had the spots. Children examined had a mean age of 8.5 years, 54% were boys, and 98% were white. The children with spots had a mean age of 8.0 years, 54% were boys, and 100% were white.

The following variables were not associated with a child having black spots: gender, school attended, type of dwelling, smoking in the home, type of home heating, frequency of bathing or shampooing, total hours of outdoor activities, walking or driving to school, swimming, wearing a hat, taking medication, and use of hairspray products. The homes of case students were marked on a map of Green River; case students lived in all parts of the school district without apparent clustering in any area. Siblings who attended other schools did not have the spots, and parents reported that children who graduated to middle school (a different building) stopped having spots. At the index school, children in the first grade had the highest prevalence of spots (77%) and children in the third grade had the lowest (17%). In attempting to explain this difference, we found that all grades played together during recess, but the two third-grade classes and one fourth-grade class lined up to enter the building after recess through a different entrance on the north side. Of 147 children who entered the school building after recess through the southwest entrance, 71 (48%) had spots; but only 16

Figure 1.—The photograph shows the scalp of a child with black spots, which range from 1 to 5 mm in diameter.

(24%) of 68 who entered by the north entrance had spots (odds ratio 3.0, $P < .001$). The southwest entrance is a cul-de-sac with severe wind eddies, but the north entrance is more open. On the playground near the southwest entrance, we observed small flakes of black material mixed with windblown sand. These black flakes, when applied to the head of one of the investigators and left on during vigorous exercise, produced a case of black spots.

The only nearby source of black material was the school roof, which was tar-and-gravel type, in poor repair, with large patches of exposed tarpaper. The second school also had this type of roof, also in poor repair, and similar black flakes could be found in the dirt around the school. The four other elementary schools, two middle schools, and one high school in Green River all had different roofing material. None of these schools had black material in the windblown sand. We screened children at an elementary school with a metal roof and found that only 1 (1%) of 80 students examined had black spots.

Laboratory Analysis

On microscopic examination, the black material from scalp scrapings was amorphous and homogenous. Aqueous potassium hydroxide preparations did not contain hyphae. The black material was soluble in most nonpolar organic solvents, leaving a residue of tiny white crystals. Gas chromatography and infrared spectrophotometry showed that the portion soluble in carbon tetrachloride was a complex mixture of long-chain hydrocarbons, consistent with tar.

Specimens of roof tar, black flakes from the playground, and black spots from scalps had nearly identical infrared spectra, indicating that the same tar was in all three specimens.

Follow-up

We advised the school district that black spots would disappear if the implicated roofs were sealed or replaced. This was done in early 1991. The principal of the affected school reports that no black spots have been seen since that time and that the parents are pleased with the outcome.

Discussion

We hypothesize that windblown flakes of weathered tar from the school roof landed on children's heads on the playground; in contact with scalp oils and sweat, the tar dissolved to form the characteristic spots. Tar flakes that landed on other exposed skin were probably washed off or blown off before they could dissolve.

We reviewed records from previous unsolved outbreaks in 1980 in Craig, Colorado (G. Istre, MD, written communication, December 1990), and in 1984 in Casper, Wyoming (R. Steketee, MD, Centers for Disease Control internal memo Epi-84-47-2, 1985), and found that the same mechanism was plausible. Specimens of black spots saved from the outbreak in Craig proved to be chemically similar to the tar found in Green River. Skin biopsy specimens from the investigation in Craig showed that the spots rested on the epidermis, did not invade below the surface, and had no associated inflammation. In Casper (where 1,380 cases were identified during a massive screening), maintenance records showed that all of the roofs of the affected schools were aging tar-and-gravel type when the problem occurred. We were unable to obtain specific information on outbreaks reported in 1984 in Lead, South Dakota, and Thermopolis, Wyoming. After this investigation, a similar outbreak in Shelby, Montana, affected 70% of 234 students at two schools. Windblown tar was again shown to be the cause (T. Damerow, PhD, State Epidemiologist, Montana Department of Health and Environmental Sciences, written communication, April 1992).

Why has this problem surfaced only in towns in the mountainous West? In areas with little rain, roofs are not replaced frequently; the roofing material on the school in our study was 19 years old. Intense high-altitude sunlight may degrade tar to a friable condition; then the high winds of the Continental Divide blow the tar flakes from the roofs. Most towns with reported cases of black spots lie in or near the "Wyoming wind corridor," an area of strong and consistent winter winds.[1]

Community anxiety about apparent disease clusters can grow out of proportion to the level of morbidity actually experienced.[2] The condition reported here does not meet the definition of any known disease, and no one was at risk for death or disability from black spots. Yet, as any local health officer can attest, situations like this can cause a great deal of community concern and can lead to expensive and disruptive attempts at diagnosis and remediation. Our investigation came about in response to strong parental pressure on the school system, which was then transmitted to the state health department.

We estimate the cost of this investigation was $5,000, which includes travel, materials, and salaries. The laboratory analysis was performed at no charge by the Department of Chemistry of Western Wyoming College. Some investigations cost much more, depending on the personnel required and the extent of laboratory analysis. A decision about whether to mount an investigation should include a consideration of the cost of an investigation versus the cost of alternatives, such as school closures or inconclusive visits to physicians for affected children, and the value to a community of finding an answer to a frustrating and worrisome problem.

When is an environmental investigation indicated? One manual[3] suggests that an unusual number of cases of a rare condition, biologically plausible exposures, or intense community concern probably justify further study. In this epidemic of black spots, the high prevalence of the condition and the homogeneity of cases indicated a cluster that could probably be solved by epidemiologic methods, even though previous investigations had been inconclusive. Investigations of noninfectious disease clusters are often frustrating and difficult to bring to closure; we hope this account of a successful one will encourage others who encounter similar problems.

Acknowledgment

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Articles

Physicians' Adjustment to Retirement

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We address the questions, How do physicians adjust to and enjoy their retirement? What factors contribute to the well-being of retired physicians? A 60-item questionnaire mailed to 238 retired physicians in Los Angeles County with a 41.6% response rate assessed health, standard of living, relationships, activities, emotional difficulties, and general enjoyment. Health often improved after retirement, as did relationships with spouses and children. Standard of living was comfortable or better for most. Retired physicians engage in a wide range of interests and activities. Emotional difficulties are minimal and considerably reduced after retirement. Most physicians enjoy the freedom and activities of retirement and are happy. Fears of boredom and deterioration are unfounded.

(Virshup B, Coombs RH: Physicians' adjustment to retirement. West J Med 1993 Feb; 158:142-144)

Whereas retirement a generation ago was scarcely considered an alternative except when physically mandated, today more and more physicians, disturbed by the increasingly onerous atmosphere of medical practice, are thinking about retirement. For most physicians, the contemplation of retirement generally is not pleasant. On the one hand, their removal from a profession that has preoccupied them intellectually and emotionally for a lifetime leaves them without important sources of personal gratification and validation. On the other is a popular perception of retirement as a life with nothing important to do, filled with boredom and an early death.

Relatively little is known about physician retirement—how well physicians adjust to this new phase of life, what they do with their time, and how happy they are. We found only two studies that had been done of retired physicians.[1,2]

Our study was designed to answer the following questions: How well do physicians adjust to and enjoy their retirement? and What are the factors that contribute to the well-being of retired physicians? Specifically, the study investigated their health, standard of living, relationships, activities, emotional difficulties, and general satisfaction.

Methods

A 60-item questionnaire was mailed to 238 retired physicians in Los Angeles County, chosen at random from the retired section of the Los Angeles County Medical Association Directory. At the time the questionnaire was mailed, 2,124 physicians listed in the directory had changed their status from active to retired. Of the 238, 99 (41.6%) returned usable forms. Supplementing this information, we recorded interviews with 20 of these physicians, querying them in small groups about their retirement experiences.

The following specialties were represented: obstetrics and gynecology and internal medicine, 13 each; anesthesiology, 10; general surgery, 8; general practice, 6; psychiatry and radiology, 5 each; pediatrics and family medicine, 4 each; ophthalmology, cardiology, EENT, urology, and pathology, 3 each; neurology, orthopedic surgery, and otolaryngology (ENT), 2 each; and 1 each of allergy, radiation oncology, preventive medicine and public health, and cardiovascular surgery. Six did not indicate a specialty.

The questionnaire, mostly consisting of Likert-type scale items, sought information about demographic and medical practice backgrounds. Retirement questions focused on their reasons for retiring, adjustment problems, health and well-being, and the status of their interpersonal relationships. Also included were how they spent their time and the degree of satisfaction with these activities.

Not all 99 physicians answered all questions. When percentages are cited, they are for physicians who did answer the specific question.

To assess whether the nonrespondents were similar or dissimilar to the respondents, we mailed a one-page questionnaire containing several items selected from the original questionnaire; 62 physicians responded to this mailing. Of these, 11 indicated that they had not responded to the earlier mailing because they were not fully retired. In addition, 3 had died, and 1 was incapacitated by a severe stroke.

A comparison of nonrespondents and respondents on selected items found little difference in age (72 and 71.5), male sex (96% and 91%), and preparations for retirement (27% of the nonrespondents had prepared extremely well, 52% fairly well, 13% less well, and 8% poorly; the equivalent figures for respondents were 25%, 52%, 16%, and 6%, respectively). Nonrespondents tended to be less healthy. Although a near equal number of nonrespondents (25%) as respondents (27%) reported excellent health, fewer had good health (33% of the nonrespondents and 52% of the respondents). More nonrespondents than respondents reported fair health (31% and 17%, respectively) or poor health (10% and 4%, respectively).

Nonrespondents also tended to be slightly less happy: 17% reported that life is wonderful, and another 54% were happy; 21% said life is "OK," and 8% were unhappy. The corresponding response for nonrespondents was 23%, 55%, 15%, and 7%. Yet, nonrespondents were more enthusiastic about retirement than the respondents. Of the former, 21% could recommend retirement enthusiastically; 56% said, yes, retirement is good; 21% were ambivalent; and only 2%

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could not recommend it. Contrasting figures for respondents were 18%, 48%, 27%, and 6.5%. These figures suggest that our respondents were fairly representative of the larger population from which the sample was drawn.

Results

Of the 99 respondents, 90 were men, a sex distribution representative of their generation. Their mean age was 71.5 years. Most of them (79) had retired in the past 10 years. They had practiced an average of 35 years.

Health

Physically, 27 were in excellent health, 51 in good health, 17 fair, and 4 poor. Of respondents, 25 were vigorously active, 68 were mainly or moderately sedentary, and 6 were very limited. Although 26 had mentioned poor health as a primary reason for retiring and 14 as a secondary reason, only 16 said they had a medical problem now. Of respondents, 19 said their health was better or much better, and 15 said it was worse. After retirement they had a mean weight loss of 1 kg (2.4 lb); 40 had lost weight, 35 were unchanged, and 25 had gained weight.

Standard of Living

Income was comfortable or better for 74; 22 felt it was adequate; 4 said they were just scraping by. Many (78) felt they had prepared well for retirement; 16, just so-so; 6, poorly. Most (97) lived in their own house or condo, and all were pleased with their living arrangements.

Relationships

Of respondents, 80 were married, with the others either divorced (7), separated (1), widowed (8), or single (3). Of those living with their spouse, 34% found their relationship to be improved after retiring; for only 3% it had become worse. In this sample, 27 had an inactive sex life, 38 were occasionally active, 34 moderately active, and 1 "very active."

Most retirees had two or three children; the numbers ranged from none (8) to nine (2), and 98 found their children moderately to very supportive; 30 found their relationship with their children better since retiring, and only 1 found it worse.

Of these retired physicians, 69 believed they were introverts; 30 believed they were extroverts. Although 63 said they had a functioning support group of friends, only 57 felt the group was very important to them. When these retired physicians were asked what they had liked most about practice, only 24 mentioned patient contact.

Activities After Retirement

Retired physicians in our survey found enjoyment in many activities (Table 1). Only 13 found themselves doing "nothing." Retired physicians had few severe emotional difficulties, and what problems they had seemed better after retiring (Table 2).

Of these retired physicians, 75 enjoyed their retirement, and 49 said life was better since retiring. Only 7 did not enjoy their retirement and were definitely unhappy. The most frequent reasons given for not enjoying retirement were decreased intellectual stimulation, limited income, and missing associates.

Discussion

To date there have been few studies examining the factors affecting the well-being of physicians in retirement. In a study of 58 older Canadian physicians, Grauer and Campbell[1] found that few had hobbies, friends, or even close family relationships that might fill the void of an abandoned practice. Rowe surveyed 142 physicians in the Rochester, New York, area and found that good health and adequate income were the prime factors in successful retirement, along with active involvement in postretirement activities, especially nonmedical ones.[2]

TABLE 1.—*Activities Before and After Retirement*

Activity	Frequently Engages in Activity, % (Rank Order) After	Before	Increase <Decrease> After Retirement, %
Reading	84 (1)	74 (2)	10
Recreation	75 (2)	42 (8)	33
Family activities	75 (3)	65 (3)	10
Social activities	71 (4)	61 (4)	10
Art, hobbies	60 (5)	31 (9)	29
Travel	57 (6)	43 (7)	14
Watching television	52 (7)	22 (11)	30
Yard work	47 (8)	25 (10)	22
Housework	36 (9)	19 (12)	17
Organizations	28 (10)	47 (5)	<19>
Professional activities	28 (10)	100 (1)	<72>
Doing nothing	13 (12)	7 (13)	6
Teaching	11 (13)	46 (6)	<35>

Retirement affords physicians a chance to adopt a different view of life, a view that is slower, gentler, more peaceful, yet interesting and fulfilling, a life filled with new opportunities for exploring, for doing, and for being. For some, however, the change is fraught with regret and anxiety. Said one, "I hated it at first. I was not prepared for it." And another: "You have to get over the fact that you don't have to jump when the phone rings, and you miss terribly your close associations with doctors you met over the years."

TABLE 2.—*Emotional Difficulties After Retirement*

Problem	Reports Difficulty, % Always or Often	Sometimes	Severe Difficulty, %	Difficulty Is Better Since Retirement, %	Difficulty Is Worse Since Retirement, %
Boredom	8	13	6	32	17
Loneliness	1	11	3	31	10
Depression	5	13	3	40	16
Frustration	4	10	2	48	12
Anger	2	14	0	47	8

One of the difficulties these physicians experienced was the loss of feelings of worth, of their important self-image as healer. They said, "I feel a loss. Perhaps in my self-image. [When I retired, I felt] I wasn't doing anything of much significance." "You go from being almost worshipped, and I use the word loosely, but people look up to you and they think that you're God; they know that you're not, but they hope you are because when they're sick, they want you to be, they need a miracle, they want a miracle. You go from that to going home and picking up your own dishes and taking them over to the sink." "There are times when one feels, at least I felt, that doing a few household chores and pulling a few weeds in the

front yard weren't quite as important as sewing up somebody's wounds." "Fear of retirement is the fear of losing identification as a doctor. There's a whole lot more to life. You have to get rid of your sense of identity as a physician."

Some, of course, did not succeed. But, surprisingly perhaps, most found no or little adjustment was necessary. "It took me one minute to make the change." "I went out from under a cloud into the sunlight."

When asked what they do, they responded: "For anyone who has a mind that has been working all their lives, the mind keeps working and will discover a subject upon which to work."

One of the major benefits was a change within themselves. The type A personality subsides. "I feel different internally. I'm not itchy-antsy-tense. As aggressive as I was." "I'm quite a different person than the SOB I was in those days. Now I'm only occasionally an SOB." "I get along better now with my children than I did when in practice. I remember when my oldest son graduated from high school and my kid won all the awards. I was the most surprised. I had no idea about his status in school, anything. It came as such a shock to me. All this had been going on, and I had missed it. Our relationship now is far better."

In their new awareness, some physicians looked back and advised, "If doctors devote themselves to their practice, they haven't taken full advantage of the other wonderful things in life. There are other vistas they should permit themselves to experience."

It would appear that most fears of retirement are unfounded. Retired physicians generally enjoy their retirement and find life more satisfying afterward than before. Adequate income, reasonable health, and a happy spouse would appear to be prerequisites.

The last word on retirement perhaps should go to the physician who said, "I've never been so happy and content. These are the best days of my life."

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Prevalence of Human Immunodeficiency Virus Infection in a Sample of Immigrants in the United States

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EDITOR'S NOTE: *Years ago, experts predicted that the acquired immunodeficiency syndrome would spread to every part of the world and every part of society. The articles by Studemeister and Kent and Calonge and co-workers* that follow are further evidence that this is happening. These and other articles we will publish in the next few months confirm our worst fears and challenge all of us to continue engaging in basic, applied, and behavioral research and to continue providing the very best care, ranging from prevention through hospice, with an emphasis on compassion.*

LINDA HAWES CLEVER, MD

Data from surveillance studies indicate that infection with the human immunodeficiency virus (HIV) has become highly prevalent in certain portions of the population in the United States. Population surveys show high HIV seroprevalence rates among homosexual and bisexual men and other persons at risk for HIV infection.[1] Prevalence rates of broader segments of the population, such as blood donors, applicants for military service, and patients in hospitals are generally less than 1%.[1] On the basis of such surveillance data, the Centers for Disease Control and Prevention estimates that about 1 million Americans are currently infected with HIV.[2]

Detailed information describing the prevalence of HIV infection among immigrants to the United States has not been published. Immigrants represent a sizable portion of the North American population. For example, in 1989 more than a million immigrants were granted legal permanent resident status and about 233,000 persons were naturalized to become US citizens.[3] During the 1980s, more than 6 million immigrants were granted permanent residence, totaling 2.7 immigrants per 1,000 US residents.[3] Since December 1, 1987, when the United States Congress mandated testing for HIV infection for all foreign-born persons 15 years of age and older applying for permanent resident status, through September 30, 1989, more than 3 million applicants were tested for HIV infection.[4] To clarify the HIV seroprevalence rate and patterns of HIV infection in immigrants applying for US permanent resident status in the San Jose, California, area, we analyzed demographic data and the results of HIV serologic tests of all applicants at a single local facility in San Jose during a three-year period.

Subjects and Methods

Study Population

Between January 1, 1988, and December 31, 1990, a total of 6,188 aliens applying for US permanent resident status were examined at the San Jose (California) Medical Group Clinic by designated civil surgeons. Of these 6,188, 6,023 (97%) were 15 years of age and older and underwent serologic testing for syphilis and HIV infection as required by the US Immigration and Naturalization Service.[5] Data from these 6,023 subjects seen at the San Jose Medical Group Clinic were used in our study. Informed consent was obtained from all subjects before blood specimen collection. Risk analysis for HIV was done on applicants with positive enzyme-linked immunosorbent assay (ELISA) and Western blot results. The demographic and serologic data of these 6,023 subjects were analyzed retrospectively for our study.

Laboratory Methods

Serum specimens were tested for the presence of HIV antibodies by the ELISA method at a commercial laboratory. Serum that was reactive by ELISA was tested again using the same method. Those specimens that were repeatedly reactive were confirmed by the Western blot method. Western blot assays were considered positive if any two of viral protein bands p24, gp41, or gp120/160 were present.[6] An indeterminate result was considered to be the presence of any other band or bands that failed to meet the positive criteria and a negative result the absence of all bands. Persons with indeterminate Western blot assays were retested within six months. Syphilis testing was done by the rapid plasma reagin test (RPR) for screening and the fluorescent treponemal antibody absorption test for confirmation.

Statistical Analysis

Statistical analyses were done by χ^2 with Yates's continuity correction or, where appropriate, two-tailed Fisher's exact test. Confidence intervals (CI) for relative risks (RR) were performed using Miettinen's test-based method.[7]

Results

Table 1 shows the demographic characteristics of the 6,023 consecutive immigrants 15 years of age and older applying for permanent residence. Their median age was 31

*B. Ned Calonge, MD, Lyle R. Petersen, MD, Rebecca S. Miller, MS, and Guillermo Marshall, PhD, "Human Immunodeficiency Virus Seroprevalence in Primary Care Practices in the United States," pp 148-152 of this issue.

(Studemeister AE, Kent GP: Prevalence of human immunodeficiency virus infection in a sample of immigrants in the United States. West J Med 1993 Feb; 158:145-147)

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This study was presented in part at the Sixth International Conference on AIDS, San Francisco, California, June 22, 1990.

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
ELISA = enzyme-linked immunosorbent assay
HIV = human immunodeficiency virus
RPR = rapid plasma reagin [test]
RR = relative risk

years (range 15 to 92); 3,070 (51%) were men. Latin America (36.3%) and Asia (31.8%) were represented most frequently.

As shown in Table 2, ten (0.17%) immigrants were seropositive for HIV antibodies; nine were men. All HIV-seropositive immigrants had Western blot assays that demonstrated positive bands for at least p24, gp41, and gp120/160. Men were significantly more likely than women to be HIV seropositive (RR = 8.7, 95% CI = 1.2, 62.0; Table 3).

All HIV-seropositive subjects were asymptomatic. Their median age was 33.5 years (range 21 to 39), not significantly different from the study population. Those aged 30 to 34 had the highest HIV seroprevalence (0.45%). Identified risk factors for HIV infection among male subjects included homosexual contact (7) and multiple heterosexual partners (1). The single female subject's reported risk factor was a blood transfusion. The results of risk factor analysis for one HIV-seropositive applicant were not available. Risk factors for HIV infection were not ascertained from HIV-seronegative subjects.

By racial or ethnic origin, the HIV antibody prevalence rate was as follows: black, 0.89%; Hispanic, 0.27%; white, 0.14%; and Asian, 0.05%. The HIV seroprevalence rate varied depending on the region of origin, from a low of 0.05% in applicants from Asia to a high of 2.44% in persons from the Caribbean. Although black immigrants appeared more likely to be HIV-seropositive (RR = 6.5, 95% CI = 0.9, 44.9), this was not statistically significant ($P = .051$; Table 3).

Persons with syphilis seropositivity were more likely to be seropositive for HIV (RR = 43.3, 95% CI = 16.6, 112.8; Table 3). Serologic tests were positive for syphilis in 59 (0.98%) applicants; 19 (32%) were women, 9 (47%) of whom were younger than 40 years. All immigrants with syphilis seropositivity had asymptomatic latent infection.

TABLE 1.—*Demographic Characteristics of 6,023 Immigrants Applying for United States Permanent Resident Status, San Jose, California, 1988 to 1990*

Characteristic	Immigrants No.	Immigrants (%)
Age, yr		
Median (range)	31.0	(15-92)
Mean	35.3	
Sex		
Male	3,070	(51.0)
Female	2,953	(49.0)
Racial or ethnic group		
Hispanic	2,204	(36.6)
Asian/Pacific Islander	1,918	(31.8)
Other	960	(15.9)
White	717	(11.9)
Black	224	(3.7)
Region of origin		
Latin America	2,189	(36.3)
Asia	1,918	(31.8)
Middle East	588	(9.8)
Europe	580	(9.6)
Other*	509	(8.5)
Africa	198	(3.3)
Caribbean	41	(0.7)

*For descriptive purposes, immigrants from the following countries were placed in a separate category because there were no accepted standards for classifying them. India, Bangladesh, Pakistan, Afghanistan, Egypt, Turkey, former Soviet Union, Canada, Iceland, Australia, and Oceania

Discussion

Our study shows a 0.17% prevalence of HIV infection among a consecutive group of immigrants applying for US permanent resident status. The observed rate is similar to the HIV seroprevalence rate of 0.13% reported for more than 300,000 immigrants in 1988.[4] These data suggest that the rate of HIV infection among immigrants applying for US permanent residence is comparable to, if not less than, that of the general American population. The US rate may be lower in part because the denominator includes those persons younger than 15 years of age, relatively few of whom are infected with HIV. The observed rate in our sample was higher than that of blood donors (0.0084%) and military service applicants (0.12%), which exclude persons at increased risk of HIV infection.[1] On the other hand, it was much lower than the seroprevalence rates of persons in high-risk groups, such as homosexual men and intravenous drug injectors.[1]

TABLE 2.—*Human Immunodeficiency Virus (HIV) Antibody Status According to Sex, Age, Racial or Ethnic Group, and Region of Origin for Applicants for US Permanent Residence Status, San Jose, California, 1988 to 1990*

Characteristic	No. HIV-Positive/ No. Tested	(%)	95% CI (%)
Total	10/6,023	(0.17)	0.06, 0.27
Sex			
Male	9/3,070	(0.29)	0.10, 0.48
Female	1/2,953	(0.03)	0.00, 0.10
Age, yr			
15-19	0/244	(0.00)	
20-24	1/763	(0.13)	0.00, 0.39
25-29	1/1,354	(0.07)	0.00, 0.22
30-34	6/1,343	(0.45)	0.09, 0.80
35-39	2/642	(0.31)	0.00, 0.74
>39	0/1,394	(0.00)	
Racial or ethnic group			
Black	2/224	(0.89)	0.00, 2.12
Hispanic	6/2,204	(0.27)	0.05, 0.49
White	1/717	(0.14)	0.00, 0.41
Asian/Pacific Islander	1/1,918	(0.05)	0.00, 0.15
Other	0/960	(0.00)	
Region of origin			
Caribbean	1/41	(2.44)	0.00, 7.16
Africa	1/198	(0.51)	0.00, 1.49
Latin America	6/2,189	(0.27)	0.06, 0.49
Europe	1/580	(0.17)	0.00, 0.51
Asia	1/1,918	(0.05)	0.00, 0.15
Middle East	0/588	(0.00)	
Other*	0/509	(0.00)	

CI = confidence interval

*For descriptive purposes, immigrants from the following countries were placed in a separate category because there were no accepted standards for classifying them. India, Bangladesh, Pakistan, Afghanistan, Egypt, Turkey, former Soviet Union, Canada, Iceland, Australia, and Oceania.

Certain selection and information biases may limit our ability to generalize our findings, in that our sample represented only a fraction of the total number of immigration visa applicants in the United States. In comparison, during the same time period of our study (1988 to 1990), a total of 3,270,432 immigrants were granted permanent resident status in this country. Their regions of origin were as follows: Latin America, 50.2%; Asia, 24.4%; Caribbean, 9.7%; Europe, 8.0%; Middle East, 3.5%; and Africa, 2.4%.[3,8] Thus, our sample consisted of lower proportions of immigrants from Latin America and the Caribbean (Table 1). Moreover, our results may underestimate the true HIV seroprevalence rates of the immigrant population because of the discouragement of immigrants who think that they may be HIV seropositive from participating in the legal application process, which involves mandatory HIV testing.

TABLE 3.—*Risk Factors for Human Immunodeficiency Virus (HIV) Infection in Applicants for US Permanent Residence Status, San Jose, California, 1988 to 1990*

Characteristic	No. HIV-Positive/Total	(%)	RR (95% CI)		P
Syphilis serologic test					
Positive	3/59	(5.08)	43.3	(16.6, 112.8)	<.001
Negative	7/5,964	(0.12)			
Sex					
Male	9/3,070	(0.29)	8.7	(1.2, 62.0)	.022
Female	1/2,953	(0.03)			
Racial or ethnic group					
Black	2/224	(0.89)	6.5	(0.9, 44.9)	.051
Other	8/5,799	(0.14)			

CI = confidence interval, RR = relative risk

The observed rate of HIV seroprevalence in our study varied depending on the region of origin, with the highest rates occurring among immigrants from the Caribbean (2.44%) and the lowest rates among those from Europe (0.17%) and Asia (0.05%). Our findings do not necessarily reflect HIV seroprevalence rates of the regions of origin of our immigrants, some of whom may have acquired the infection while residing in the United States. The US Immigration and Naturalization Service estimates that the typical legalized immigrant has lived in the United States for ten years.[8]

The pattern of HIV infection in our group of immigrants was comparable to that of the general American population in that higher rates of HIV seroprevalence were found among young men and blacks. Surveillance studies of military service applicants and potential blood donors in the United States indicate significantly higher rates of HIV infection among young men and certain racial and ethnic groups.[9,10] Well-recognized risk factors for HIV infection were found in our HIV-seropositive immigrants, including homosexual activity, multiple heterosexual partners, and blood transfusion.

We found a significant correlation between HIV infection and serologic tests positive for syphilis in our immigrant population. These findings may reflect that syphilis seropositivity is a marker for high-risk behavior or the increased efficiency of the sexual transmission of HIV in persons with ulcerative genital disease.[11] Close to half of women with RPR seropositivity were of childbearing age, pointing to the importance of prenatal screening for syphilis.

The current US immigration policy of mandatory HIV serologic screening and the denial of permanent resident status to immigrants with HIV infection is controversial in that possible benefits from an economic or medical standpoint also invoke ethical dilemmas. From a medical perspective, serologic screening for HIV infection may be beneficial, given recent recommendations for early intervention with zidovudine therapy and prophylaxis against *Pneumocystis carinii* pneumonia, which underscore the importance of identifying HIV infection before symptoms are present.[12,13] In addition, the current application process discourages the self-identification of risk factors for HIV infection. Some may also argue that preventing HIV-infected persons from remaining in this country may have economic and public health benefit. From an ethical standpoint, however, opponents to a policy of mandatory HIV testing are justifiably concerned with the lack of appropriate safeguards to maintain confidentiality, access to health care, and employment. Given the fact that most of these applicants have been in this country for several years and therefore may have become infected in the United States, the practice of denying permanent residence to those with positive antibody tests may result in forced expatriation to countries where adequate medical therapy for HIV infection is not available. Until these issues are resolved, civil surgeons conducting examinations of immigrants must be prepared to offer appropriate education, counseling, and referral to medical treatment for persons found to be infected with HIV.

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Articles

Human Immunodeficiency Virus Seroprevalence in Primary Care Practices in the United States

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The incidence of the acquired immunodeficiency syndrome (AIDS) in the United States is well described by the AIDS reporting system of the Centers for Disease Control and Prevention (CDC).[1] An estimation of the underlying rates and trends of infection with the human immunodeficiency virus type 1 (HIV-1), however, required monitoring of seroprevalence rates from several different sources, with consideration of the possible biases and limitations inherent in each source. Seroprevalence surveys conducted in sentinel hospitals,[2] military service applicants and personnel,[3-6] Job Corps entrants,[7] blood donors,[8,9] and mothers of live infants[10] provided information for estimating HIV-1 infection rates in these populations. Some of these groups were possibly biased by self-selection, and all were limited by a focus on population characteristics, such as persons of specific age and gender, persons choosing or experiencing specific careers or activities, or persons requiring admission to a hospital.

This study, a collaborative effort between the CDC and the Ambulatory Sentinel Practice Network, Inc (ASPN), estimated the seroprevalence of HIV-1 infection in persons seeking medical care from primary health care providers. The ASPN is a volunteer practice-based primary care research network that began collecting data in 1982 and currently includes 72 practices in the United States and Canada with 334 primary care clinicians, 90% of whom are family physicians.[11] The network has an active patient population (last clinical visit within the previous two years) of about 350,000. The combined ASPN patient population from US practices does not differ significantly from the general US population in age and sex distribution.[12] Only the US practices were eligible to participate in the project, and 44 volunteered to conduct the investigation.*

A primary care practice-based research network like ASPN provides an important opportunity to determine HIV-1 seroprevalence in a population of patients seeking outpatient primary care from front-line clinicians. Information from this survey has direct implications for primary care clinicians in the United States and allows for a comparison with seroprevalence rates from other special subpopulations. The data collection methods used in this study also allow for a unique estimation of seroprevalence in terms of clinician-recognized or unrecognized HIV-1 infection risk factors. In this article we discuss the data collected during the first 19 months of the project, from June 1, 1989, to December 31, 1990.

Subjects and Methods

Ambulatory Sentinel Practice Network Population

The ASPN patient population consists of persons who, in the previous two years, have sought ambulatory medical care from participating primary care practices in ASPN. These persons are enumerated and categorized in the practice's age-sex register. The methods involved in collecting data for the age-sex register and the use of this information as denominator data are discussed elsewhere.[12]

In Figure 1 the age-sex register for participating practices is compared with the age and sex distribution of the United States. Men 15 to 34 years of age are underrepresented in the ASPN population, whereas women 25 to 49 years of age are overrepresented. In Figure 2 the age-sex distribution of the study sample is compared with the same distribution for

*Participating practices: Foothills Family Medical Group, Auburn, California; Marny Eulberg, MD, Denver, Colorado; Mountain/Plains Family Practice, Denver, Colorado; Orchard Family Practice, Englewood, Colorado; Northern Colorado Family Medicine, Greeley, Colorado; James Andersen, MD, Fort Lauderdale, Florida; Domingo Gomez, MD, Hialeah, Florida, Family Medicine Associates, Miami, Florida; Titus Taube, MD, Warner Robins, Georgia; Steven Rothschild, MD, Chicago, Illinois; Vinton Family Medical Center, Vinton, Iowa; Linda Stewart, MD, Baton Rouge, Louisiana; Fitchburg Family Practice Residency Program, Fitchburg, Massachusetts; Peter Barker, MD, Swampscott, Massachusetts; Bay de Noc Family Health Center, Escanaba, Michigan; Eagle Medical, Excelsior, Minnesota; David Beaufait, MD, and Mark Parker, MD, Enfield, New Hampshire; Richard Douglass, MD, Hillsboro, New Hampshire; Manchester Family Health Center, Manchester, New Hampshire; Monroe Clinic, Monroe, New Hampshire; A. John Orzano, MD, Flemington, New Jersey; Central Square Health Services Center, Central Square, New York; Aurora Medical Center, Aurora, North Carolina; Bakersville Community Medical Clinic, Bakersville, North Carolina; Cape Fear Family Medical Care, Fayetteville, North Carolina; Enid Family Medicine Clinic, Enid, Oklahoma; Madill Medical Associates, Madill, Oklahoma; Audrey Paulman, MD, Omaha, Nebraska; Dunes Family Health Care, Inc, Reedsport, Oregon; Highland Physicians, Ltd, Honesdale, Pennsylvania; Family Medical Associates, Richburg, South Carolina; Tri-County Health Care, Inc, Wessington Springs, South Dakota; Michael Hartsell, MD, Greeneville, Tennessee; Family Medical Center, Lenoir City, Tennessee; Decatur Family Clinic, Decatur, Texas; Myers & Caplan Family Medicine, Mansfield, Texas; Isaac Kleinman, MD, Rosenberg, Texas; Community Health Center, Enosburg Falls, Vermont; The Health Center, Plainfield, Vermont; Edward M. Friedler, MD, Annandale, Virginia; Beaverdam Family Practice, Beaverdam, Virginia; Physician-to-Families, Inc, Daleville, Virginia; Lynchburg Family Practice Residency, Lynchburg, Virginia; June Tunstall, MD, Surry, Virginia; James Ledwith, MD, Tappahannock, Virginia; Cle Elum Family Medicine Center, Cle Elum, Washington; Eglon Clinic, Eglon, West Virginia; De Forest Area Medical Clinic, De Forest, Wisconsin; Kronenwetter Clinic, Mosinee, Wisconsin; Doctors Park Family Physicians, Platteville, Wisconsin; Terry Hankey, MD, Waupaca, Wisconsin. Board of Directors: Lorne A. Becker, MD; Eugene S. Farley, Jr, MD; William L. Freeman, MD; Jack Froom, MD; Larry A. Green, MD; Curtis Hames, Sr, MD, John Hickner, MD; William Hogg, MD; Jack Kirk, MD; Walt Rosser, MD; Milton H. Seifert, Jr, MD; Richard Wasserman, MD; Maurice Wood, MD.

(Calonge BN, Petersen LR, Miller RS, Marshall G: Human immunodeficiency virus seroprevalence in primary care practices in the United States. West J Med 1993 Feb; 158:148-152)

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
ASPN = Ambulatory Sentinel Practice Network, Inc
CDC = Centers for Disease Control and Prevention
CI = confidence interval
HIV-1 = human immunodeficiency virus type 1
NAMCS = National Ambulatory Medical Care Survey
SMSA = Standard Metropolitan Statistical Area

patients visiting family physicians and general practitioners reported in the 1989 National Ambulatory Medical Care Survey (NAMCS) data.[13] Compared with the sample of patients included in NAMCS, the sample of ASPN patients having blood drawn tended to include more women older than 24 years and fewer men younger than 35 years.

Based on data collected when each practice joined the ASPN, individual ASPN practices are categorized as serving nonrural or rural communities (using Standard Metropolitan Statistical Area [SMSA] criteria). Table 1 describes the geographic distribution of ASPN practices by US Bureau of Census regions and includes data regarding rural versus nonrural practice settings. Most study practices are located in the New England, South Atlantic, and Midwest states, and 66% of the total practices are in non-SMSA communities.

Study Sample—Specimen Eligibility and Selection

Patients aged 15 to 49 years who had blood drawn for clinical purposes were eligible for inclusion in the study. This age range was selected to focus on age groups with the highest risk for HIV-1 exposure. The study sample included all persons who had blood drawn during a specimen-testing month. Specimen-testing months were scheduled an average of once every three months and were selected to represent all seasons and to be convenient for the practices.

Data and Specimen Collection

When a blood specimen was drawn for a clinical test ordered for an eligible patient, the clinician completed a study information card that included patient demographics, clinician-perceived HIV-1 infection risk information, clinical information relating to the patient's known HIV-1 status, and whether the test was ordered specifically to evaluate the patient's HIV-1 status. To comply with the requirements of the unlinked protocol, patients were not queried directly about their HIV-1 status. This method reduced the possible self-selection bias that might exist if informed consent had been obtained.[14] Completed cards were sent to the ASPN central office. Blood specimens in excess of that required for

TABLE 1.—*Ambulatory Sentinel Practice Network, Inc Practices and US Census Regions*

Region	States	Practices, No.	Rural (Non-SMSA) Practices, No. (%)
1....	Maine, Vermont, Rhode Island, Massachusetts, Connecticut, New Hampshire	8	5 (62)
2....	New York, New Jersey, Pennsylvania	3	3 (100)
3....	Michigan, Wisconsin, Illinois, Ohio, Indiana	6	5 (83)
4....	Minnesota, Iowa, Missouri, North Dakota, South Dakota, Nebraska, Kansas	3	2 (67)
5....	Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Georgia, Florida	12	8 (67)
6....	Kentucky, Tennessee, Mississippi, Alabama	2	2 (100)
7....	Oklahoma, Arkansas, Louisiana, Texas	4	1 (25)
8....	Montana, Idaho, Wyoming, Nevada, Utah, Colorado, New Mexico, Arizona	3	0 (0)
9....	Alaska, Washington, Oregon, California, Hawaii	3	3 (100)

SMSA = Standard Metropolitan Statistical Area

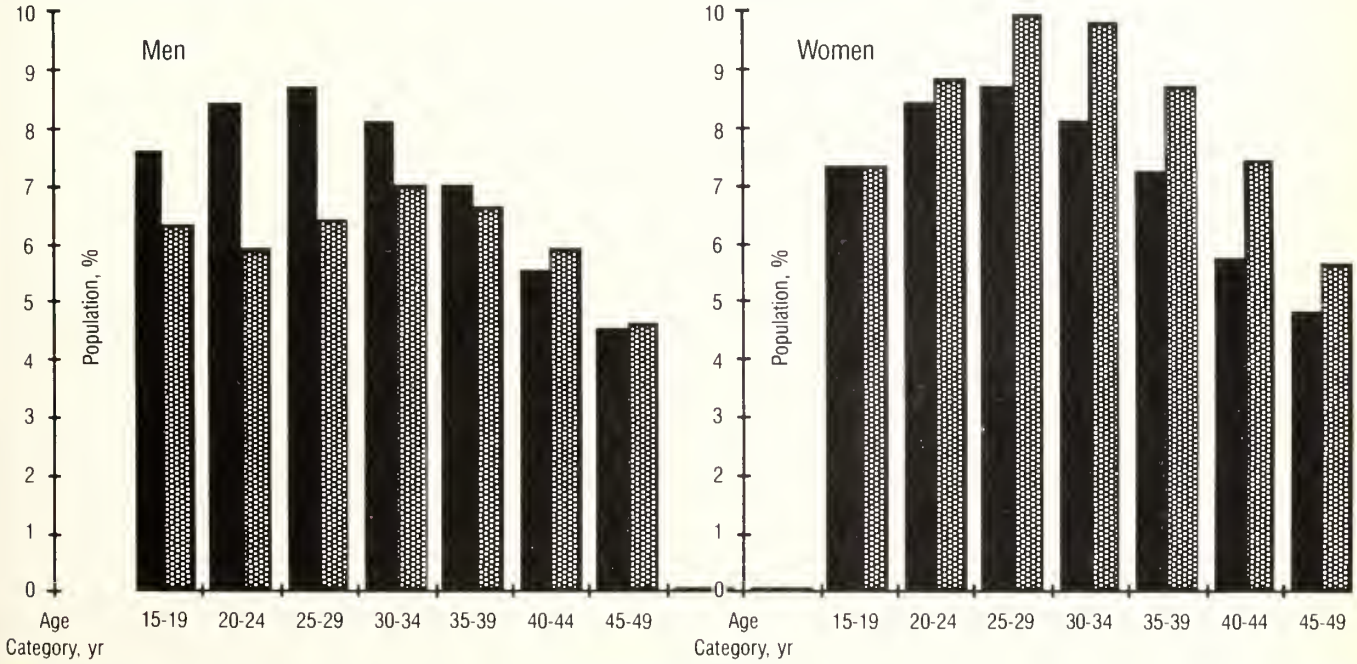

Figure 1.—The graphs show the age and sex distribution of the US population **(black bars)** and the population of the study practices for the Ambulatory Sentinel Practice Network, Inc (ASPN) **(stippled bars).**

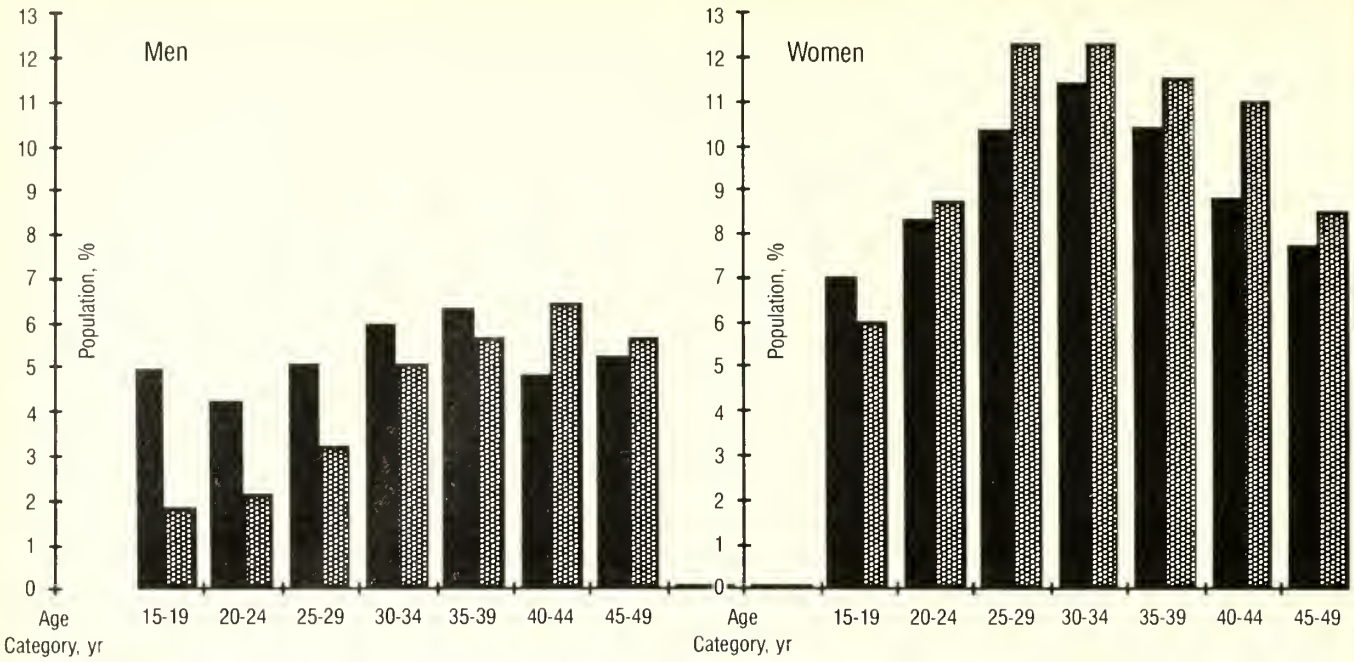

Figure 2.—The graphs show the age and sex distribution of the 1989 National Ambulatory Medical Care Survey (NAMCS) population for family and general practitioners **(black bars)** and of the study sample **(stippled bars).**

the clinical test were sent separately to the ASPN central office for HIV-1 testing. Data from blood tests were linked to card data using a unique identifier that cannot be associated with an individual patient, and results were entered into the data base by geographic area only. In addition, a random 2% of all specimen and card data was eliminated from the study data base to ensure uncertainty regarding whether a person was included in the study. Methods for primary care surveillance have been described elsewhere.[15]

HIV-1 Serologic Testing

All specimens were screened for HIV-1 antibody at a single laboratory using an enzyme immunoassay licensed by the Food and Drug Administration. Repeatedly reactive specimens were tested by Western blot and considered positive in the presence of two of three antibody bands to p24, gp 41, and gp120/160 gene products.[16]

Analysis

Crude seroprevalence rates were computed using the number of HIV-1–positive specimens and the total number of specimens in a given age, sex, race, or HIV-risk category. Adjusted seroprevalence rates were calculated by weighing the specimen results by the number of specimens contributed by each practice and by the total number of patients in each practice, accounting for age and sex distributions. The 95% confidence intervals (CI) were obtained using variance estimates that accounted for the adjusted rate calculation.

The distribution of ASPN patients by race and risk factors for infection was not available, and estimates of these distributions could be substantially influenced by sampling biases. Thus, it was not feasible to weigh the seroprevalence estimates for race and risk-factor categories adjusting for differences among practices, and only crude rates and confidence intervals are reported.

Seroprevalence rates for the entire network and for rural and nonrural categories were calculated for the total study population, for the population excluding known HIV-1–infected persons and those being tested for HIV-1 infection, and for the population with the additional exclusion of persons who were recognized as being at risk. Again, adjusted rates for nonrural versus rural and infection status categories were calculated by weighing the test results by the number of specimens per practice and the number of patients in each practice, accounting for age and sex.

Results

The results are presented from the 44 US practices that volunteered to participate and that collected data for a minimum of ten weeks during the study period (June 1, 1989, to December 31, 1990). The number of reporting weeks per practice, which varied because of scheduling, averaged 20.6 weeks with a standard deviation of plus or minus 4.9 weeks. Data from the age-sex registers for participating practices indicated an average of 2,653 persons 15 to 49 years of age per practice, with a total of 116,712 persons aged 15 to 49 years.

Data were collected from 9,747 persons. Of these, 179 (2%) were excluded as part of the blinding strategy, 233 had no serum specimens submitted with the demographic data, 114 had insufficient serum for HIV-1 testing, 140 did not have demographic data submitted with the serum specimen, and 5 did not want their blood to be used for research. Thus, 9,076 persons (93% of the original sample) were included in the final analysis.

Blood specimens from 25 (2.8 per 1,000) persons had HIV-1 antibody. Of the 25, 18 were men and 7 were women. Blood specimens from these 25 persons were obtained from 12 (27%) study practices that contributed 35% of the study sample. After adjusting the data to correct for the variable sampling duration and patient-population size of the participating practices, the seroprevalence was 2.3 per 1,000 (CI 1.3 to 3.3). Persons aged 30 to 34 years, men, minorities, and nonrural practices had the highest seroprevalence rates (Table 2).

The blood specimens used for 2 of the 25 seropositive

persons originally were drawn for linked HIV testing. Also, 13 other seropositive persons were known to have HIV-1 infection when the serum specimens were obtained; 7 of these 13 persons met the CDC case definition for AIDS. Therefore, 10 (40%) of the 25 seropositive persons, or 1.1 of every 1,000 ASPN patients, had HIV-1 infection unrecognized by their clinicians. The adjusted rate was 1.0 per 1,000 (CI 0.3 to 1.7).

Of the ten seropositive persons with unrecognized HIV-1 infection, five were men, two of whom were known by their clinicians to have had sexual contact with other men. The other three men were not considered by their clinicians to be at risk for acquiring HIV-1. All five of the women with unrecognized HIV-1 infection were likewise not considered by their clinicians to be at risk for HIV-1 infection.

Discussion

Approximately 2.3 of every 1,000 ASPN patients 15 to 49 years of age had HIV-1 infection, and 1.0 per 1,000 ASPN patients had HIV-1 infection unrecognized by their clinicians. This finding has important implications for primary care clinicians, especially in regard to their approach to HIV-1 testing. The results suggest that among the 116,712 ASPN patients 15 to 49 years of age, 268 were HIV-infected and, of those, 128 have HIV-1 infection undetected by their clinicians; therefore, 32% of all infected persons had no risk factors recognized by their clinicians. These data indicate that primary care clinicians must obtain risk-factor information from their adult patients, especially those in the age category 20 to 49 years, and should strongly encourage HIV-1 screening for all patients determined by history to be at risk for infection. Such actions are essential both for the appropriate medical care of infected persons and for the possible prevention of spread to others. There are limitations to obtaining risk status information from patients, however. Many patients are unwilling to discuss these personal matters, and others may not know they have been at risk.

Although this study provides the only source of HIV-1 epidemiologic data available for primary care patients, the results can be generalized beyond the study population only

TABLE 2.—*Patient Characteristics and HIV Seroprevalence Rates*

	Persons Tested		*Crude*	*Adjusted*	
	No.	*(%)*	*Rate/1,000*	*Rate/1,000**	*95% CI*
Age, yr					
15-19	681	7.5	0.0	0.0	--
20-24	961	10.6	2.1	3.5	0.0-9.8
25-29	1,368	15.1	3.7	4.7	0.0-9.4
30-34	1,529	16.8	7.2	7.4	2.6-12.2
35-39	1,511	16.6	2.6	1.9	0.1-3.6
40-44	1,533	16.9	1.3	0.6	0.0-1.3
45-49	1,386	15.3	0.0	0.0	--
Missing data	107	1.2	--	--	--
Sex					
Women	6,343	69.9	1.1	1.2	0.0-2.4
Men	2,712	29.9	6.6	4.6	2.5-6.7
Missing data	21	0.2	--	--	--
Race					
White (excluding Hispanic)	7,972	87.8	1.7	--	1.0-3.0
Black (including black Hispanic)	518	5.8	5.8	--	1.5-18.3
Hispanic (excluding black Hispanic)	314	3.6	22.3	--	9.8-47.4
Asian	93	1.0	10.8	--	0.6-66.9
Other	77	0.1	0.0	--	--
Missing	102	1.1	--	--	--
Practice location					
Rural (non-SMSA)	4,871	53.7	1.2	1.3	0.2-2.4
Nonrural (SMSA)	4,205	46.3	4.6	4.5	2.3-6.6
Reason for ordering blood test					
HIV testing	165	1.8	12.2	--	--
Risk factor†					
Homosexual	47	0.5	210	--	110-360
Bisexual	7	0.1	140	--	7.5-580
Drug injector	52	0.6	77	--	25-190
Transfusion‡	40	0.4	0.0	--	--
Hemophiliac	0	0.0	--	--	--
Born in Haiti or Africa	9	0.1	0.0	--	--
Other§	129	1.4	16	--	4.1-90
No known risk	8,792	96.9	0.9	--	0.4-2.0

HIV = human immunodeficiency virus, SMSA = Standard Metropolitan Statistical Area

*Adjusted for practice size and sampling and, where appropriate, age and sex distribution.

†Recognized by clinician.

‡Received blood transfusion between 1977 and 1982.

§Includes clinician-defined sources of excess risk, such as high-risk sexual partner, high-risk profession, history of needle stick or similar exposure, history of other sexually transmitted disease(s), history of multiple transfusions outside the high-risk years, and history of organ transplants. All positive tests in this category were in persons with a high-risk sexual exposure.

with caution. The study population consisted of patients seeking care from community-based primary care medical practices participating in ASPN, and the rates of positive serologic tests were based on those patients who had blood drawn. It is unknown how representative ASPN practices are of all community-based practices and how representative patients having blood drawn are of ASPN patients in the same age category. Patients having blood drawn may be more likely to have diseases that are a result of risky behaviors, which could bias the seroprevalence rates. Thus, these results are best interpreted in view of the other sources of seroprevalence estimates. The median seroprevalence rate from the sentinel hospital study, in which patients who were admitted to the hospital for HIV-related reasons were excluded, was 0.7 per 1,000,[2] which was similar to the 1.0 per 1,000 rate in the ASPN population of patients without known HIV-1 infection. The rate from military service applicants and personnel was 1.4 per 1,000 and 1.3 per 1,000, respectively.[3-6] Also comparable to the ASPN results were those from studies of Job Corps entrants (3.6 per 1,000),[7] first-time blood donors (0.42 per 1,000),[9] and mothers of live infants (1.5 per 1,000).[11]

The predominantly rural distribution of ASPN practices is different from the predominantly urban and suburban distribution of primary care practices in the United States. The finding that HIV prevalence was 3.5 times higher in urban ASPN practices than in rural ones, however, suggests that HIV-1 is more prevalent in urban areas. This implies that primary care physicians in urban settings should be particularly vigilant in ascertaining patients' HIV risk. The importance, however, of HIV-1 infection should not be overlooked in rural areas, where the seroprevalence rate was about 1 per 1,000 and in which a third of all infections were unrecognized by the patients' clinicians.

In ASPN, men had a four times higher seroprevalence rate than women, although of the women who were HIV-1 antibody-positive, 57% had infection unrecognized by their clinicians, and none of those with unrecognized infection had identified risk factors. This was compared with the 33% of infected men with infections that were unrecognized by their clinicians, of whom a third had at least one risk factor identified by their clinicians. Particularly in women, the degree of unrecognized disease underscores the need to obtain patient risk-factor information.

This initial report indicates that adult primary care patients, particularly those 15 to 49 years of age, should be assessed for HIV-1 risk factors, and those identified as having risk factors should be counseled to be tested voluntarily for HIV-1 infection. Primary care clinicians may provide the only opportunity for the early detection of infected persons for counseling and prophylactic treatment.

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See also "Prevalence of Human Immunodeficiency Virus Infection in a Sample of Immigrants in the United States," by Alex E. Studemeister, MD, and George P. Kent, MD, on pages 145-147 of this issue.

Biomedical Science

Blood Coagulation and Its Alterations in Hemorrhagic and Thrombotic Disorders

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Presented as the Distinguished Lecture at the annual meeting of the Western Association of Physicians, Carmel, California, February 5-6, 1992.

Clinical observations have added to the understanding of basic mechanisms of blood coagulation and its alterations in certain hemorrhagic and thrombotic states. Much clinical evidence exists for concluding that the exposure of blood to tissue factor (thromboplastin) on tissue cells represents the key event initiating fibrin clot formation after tissue injury. This then results in the formation of activated factor VII (VIIa)-tissue factor complexes, which must activate both factor X and factor IX for normal hemostasis. I describe the possible clinical consequences of an aberrant function of the natural anticoagulants regulating blood coagulation—antithrombin, protein C, and tissue factor pathway inhibitor. Understanding the physiologic function of tissue factor pathway inhibitor can illuminate why hemophilic patients bleed, but many other questions remain. I briefly review the four causes for acquired disorders of the blood coagulation reactions—vitamin K deficiency, hepatocellular disease, antibodies to clotting factors, and disseminated intravascular coagulation—but limit my comments to the mechanisms that trigger the formation of antibodies to clotting factors and how these antibodies can deplete the blood of clotting factor activities. Finally, heparin is able to potentiate tissue factor pathway inhibitor function, which is a possible reason why the use of heparin but not warfarin can prevent the numerous thrombotic episodes of the Trousseau's syndrome.

(Rapaport SI: Blood coagulation and its alterations in hemorrhagic and thrombotic disorders. West J Med 1993 Feb; 158:153-161)

In 1905—87 years ago—Paul Morawitz published a monograph of historical importance on the chemistry of blood coagulation.[1] In it he summarized the experiments of the 19th century that led him, and independently Fuld and Spiro, to propose what became known as the classical theory of blood coagulation. This theory stated that four factors were needed for blood to clot. Three of the factors, prothrombin, calcium ions, and fibrinogen, were present in plasma. The fourth, thromboplastin, which is today preferably called tissue factor, was thought to be contained within cells, including the leukocytes and platelets of the circulating blood (Figure 1).*

When blood left the vessels and came into contact with wettable foreign matter, platelets and leukocytes were postulated to agglutinate and liberate tissue factor. Tissue factor then reacted with calcium salts and prothrombin to generate thrombin, which converted fibrinogen to the fibrin strands of a blood clot. Furthermore, tissue factor was postulated to be released after tissue injury from a second source, which was damaged tissue cells at the surface of a wound. This caused coagulation to occur all the more rapidly.

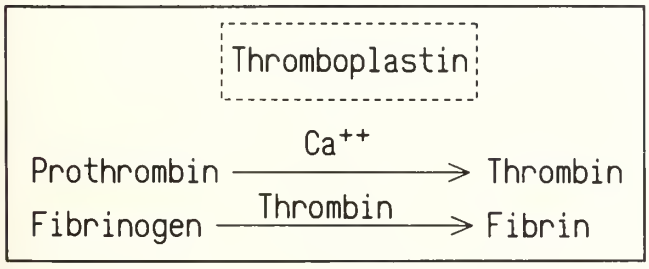

Figure 1.—In the classical theory of blood coagulation, prothrombin is converted to thrombin by the action of thromboplastin (tissue factor) in the presence of calcium ions. Thrombin then acts on the soluble fibrinogen of plasma, converting it to insoluble fibrin.

*See also "Why Does the Blood Not Coagulate?" by Oscar D. Ratnoff, MD, on pages 195-196 of this issue.

Thirty years later, in 1935, Armand Quick and coworkers developed a test based on this theory to study the coagulation defects in hemophilia and in patients with jaundice.[2] They reasoned that if they added a standardized preparation of tissue factor to recalcified plasma, then the time required for enough thrombin to form to clot the plasma would depend only on its prothrombin concentration. Therefore, their test was called a prothrombin time. It quickly entered the clinical domain in the early 1940s to monitor treatment with the newly introduced oral anticoagulant, dicumarol. The name prothrombin time has persisted until today, although we have known for more than 40 years that other clotting factors influence the test result.

Discovery of New Blood-Clotting Factors

In Figure 2 I schematically summarize my current understanding of the reactions leading to the formation of fibrin.[3] One can still find within it the classical theory: thrombin clots fibrinogen; thrombin exists in plasma as an inert precursor, prothrombin; and exposure of blood to tissue factor triggers blood coagulation. But a modern theory must be expanded to include ten additional plasma proteins that may participate in the reactions leading to the formation and stabilization of fibrin.

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ABBREVIATIONS USED IN TEXT

DIC = disseminated intravascular coagulation
TFPI = tissue factor pathway inhibitor

Furthermore, we now know that there are two ways to initiate blood coagulation. The first is, as Morawitz proposed, exposure of blood to tissue factor, which has now been identified as a glycoprotein embedded in association with phospholipid in the surface membrane of fibroblasts within and around blood vessels and in various other tissue cells. The second is the exposure of blood in vitro to a negatively charged surface. This triggers clotting not by releasing tissue factor from agglutinated platelets and leukocytes, which do not contain tissue factor within their cytoplasm, but by initiating the activation of the plasma protein referred to as Hageman factor or factor XII.

I will return to the reactions summarized in Figure 2, but I want first to describe how we got from the classical theory of Morawitz to today's understanding of blood coagulation. Physicians studying patients made many of the early steps forward. I have included a photograph of one of these physicians, Paul Owren (Figure 3), for two reasons. The first is because I have a special feeling for his memory, since I began studying blood coagulation as a Fulbright Research Scholar in 1953 in his medical department at the Rikshopital in Oslo, Norway. The second and more important reason is because his discovery of factor V, in experiments carried out with difficulty in occupied Norway during World War II and published in a remarkable monograph in 1947,[4] was the first example of what was to follow over the next 15 years. This was the discovery of one after another of new clotting factors by physicians doing what Owren had done—investigating patients whose findings could not be explained by the then-known blood clotting factors.

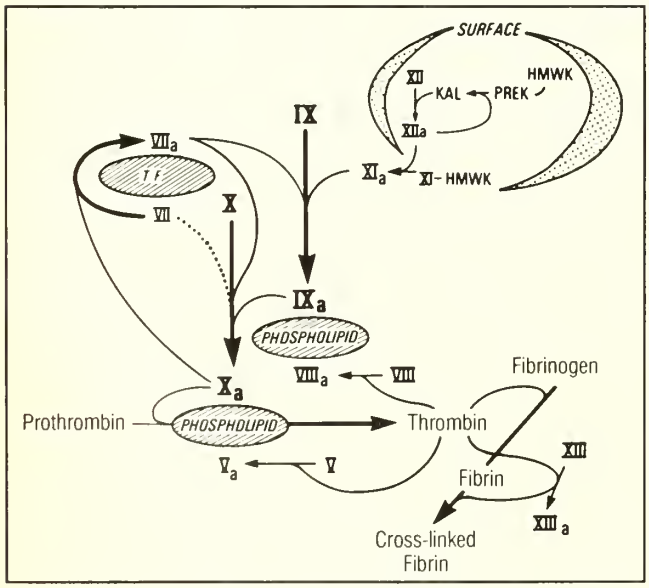

Figure 2.—The schematic representation shows the blood coagulation reactions as understood today. To avoid further complexity, the participation of calcium ions in the formation and function of all complexes, in the activation of factor IX by factor XIa, and in the activation of factor XIII has not been shown. Phospholipid is anionic phospholipid present on the surface membrane or on vesicles from activated platelets or perturbed tissue cells at a site of tissue injury (from Rapaport SI[3]). HMWK = high molecular weight kininogen, KAL = kallikrein, PREK = prekallikrein, TF = tissue factor

In the early 1900s, Thomas Addis, one of this century's foremost nephrologists, ventured briefly into blood coagulation research. He reported in 1911 that the delayed clotting of hemophilic blood could be corrected by adding a small amount of a globulin fraction from normal plasma to hemophilic blood.[5] His data were correct, but he made a mistake. Reasoning from Morawitz's classical theory (Figure 1) and knowing that hemophilic blood contained a normal amount of fibrinogen, he concluded that hemophilic blood must lack prothrombin. When others then showed that hemophilic blood contained a normal amount of prothrombin, workers in the field had a choice: either disregard Addis's data, which were no longer compatible with the classical theory, or

Figure 3.—Paul A. Owren, MD (1905-1990), was the discoverer of factor V. This photograph was taken in 1954.

change the theory. They chose the former, and Addis's data were quickly forgotten. A quarter of a century later, in 1936, Patek and Taylor repeated Addis's experiment and showed again that a material in the globulin fraction of normal plasma, to which they gave the name antihemophilic globulin and which today we call factor VIII, corrected the defective clotting of hemophilic blood.[6] It was then assumed that all hemophilia—that hereditary, life-threatening bleeding disease affecting only the male sex because it is transmitted as an X chromosome-linked genetic disorder—stemmed from a deficiency of factor VIII.

It was a shock to learn in 1952 that hemophilia was not a single disease. The most common form, hemophilia A, did indeed result from factor VIII deficiency, but some patients with hemophilia bled because they lacked a different clotting factor activity. These patients had hemophilia B, and their blood was deficient in factor IX.

Three groups recognized the existence of hemophilia B at about the same time: Paul Aggeler and his colleagues at the University of California, San Francisco; Biggs, Douglas, and Macfarlane and their co-workers in Great Britain; and

the pediatricians Irving Schulman and Carl Smith in New York. I show you Aggeler's picture (Figure 4) not only because his paper in the *Proceedings of the Society for Experimental Biology and Medicine* was the first of the three early reports of hemophilia B,[7] or because his findings were presented at the 1952 Carmel, California, meeting of the Western Society of Clinical Research (the forerunner of the combined yearly meetings at Carmel of our three clinical societies). Rather, I include his picture because he was for hematologists of my vintage in the western United States an inspiring, close-at-hand example of a physician and clinical investigator of great integrity who made a fundamental discovery from the tenacious pursuit of the meaning of an observation in a patient.

Figure 4.—Paul M. Aggeler, MD (1911-1969), of the University of California, San Francisco, was the lead author of the first report on hemophilia B. This photograph was taken in the early 1960s.

Growth of Knowledge of How the Blood-Clotting Factors Interact

As new clotting factors were discovered one after another, the challenge to blood coagulation investigators, whose ranks were now being swelled by skilled protein biochemists, was to figure out what role each factor played. A significant event occurred in 1964 when Macfarlane and Davie and Ratnoff published identical cascade or waterfall concepts of the clotting reactions initiated when plasma was exposed to a negatively charged surface (Figure 5).[8,9] This representation of the reactions was an important conceptual advance, for it described blood clotting as a sequence of amplifying reactions in which an enzyme activated a substrate, which then became an enzyme activating more molecules of the next substrate, and so forth down the reaction chain.

The first two reactions shown in Figure 5 are correct: activated factor XII does activate factor XI, and activated factor XI does activate factor IX. Most of the subsequent reactions, however, are not correct. There are two main reasons for this. The first is that not all of the plasma protein clotting factors involved in the generation of thrombin have turned out to be proenzymes. Most are proenzymes—including factor XII and factor XI and the four vitamin K-dependent clotting factors, factors VII, IX, X, and prothrombin. But others, including the two key clotting factors VIII and V, are nonenzymatic cofactors. The second

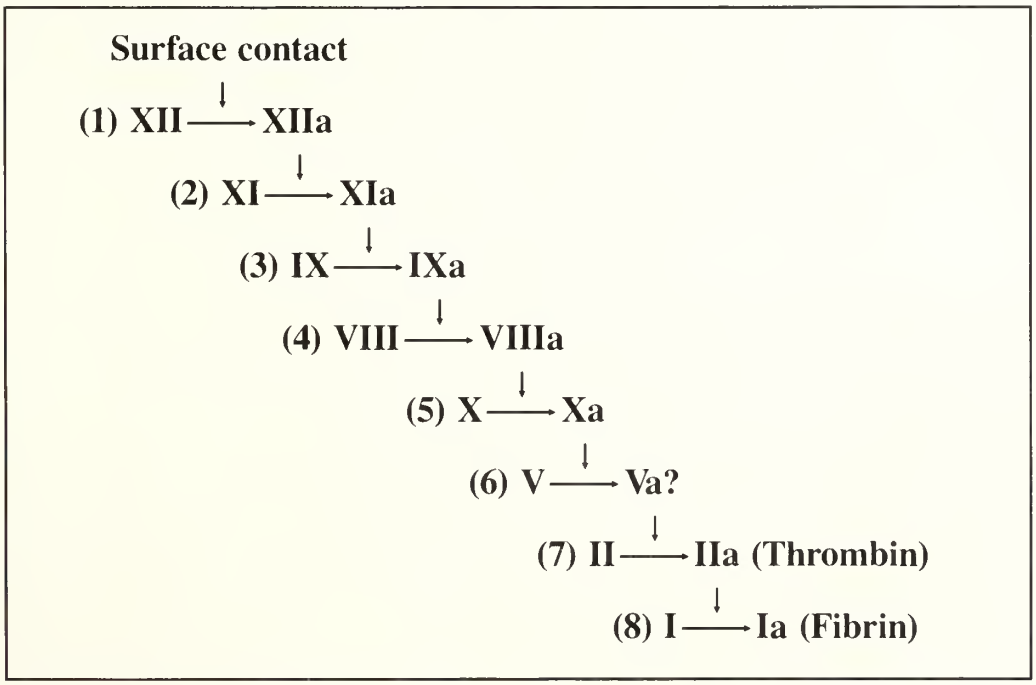

Figure 5.—The schematic representation shows the cascade or waterfall concept of the intrinsic clotting reactions proposed in 1964. The blood coagulation factors involved in the generation of thrombin were each thought to be proenzymes. The generation of thrombin was viewed as a sequence of amplifying reactions in which an enzyme activated a substrate, which then became an enzyme activating more molecules of the next substrate.

reason is that the blood-clotting reactions do not just go forward; there are also key feedback reactions.

Another concept also held reign during the 1960s and most of the 1970s. This was the belief that the two pathways for initiating coagulation—the intrinsic pathway triggered in vitro by the contact of plasma with a negatively charged surface, and the extrinsic pathway triggered by the formation

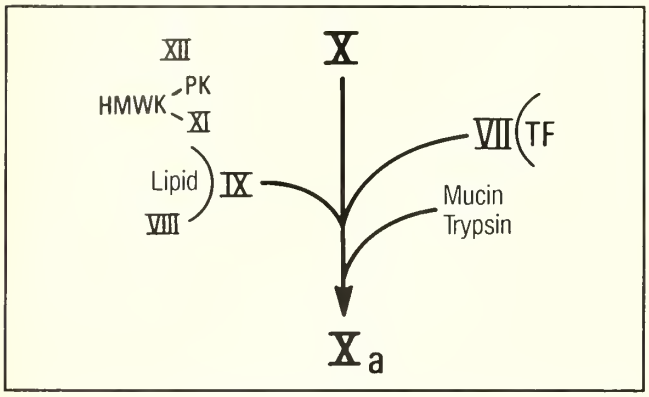

Figure 6.—The schematic representation shows the concept that the intrinsic coagulation reactions initiated by the exposure of blood to a negatively charged surface and the extrinsic coagulation reactions initiated by the exposure of blood to tissue factor (TF) first came together at the step of the activation of factor X. HMWK = high molecular weight kininogen, PK = prekallikrein

of factor VII-tissue factor complexes—first came together at the activation of factor X (Figure 6). Moreover, because the hemophilias were recognized as the most severe hereditary bleeding disorders and factors VIII and IX were thought to participate only in the intrinsic pathway, it, and not the tissue factor-dependent extrinsic pathway, was thought to be the key pathway for initiating blood coagulation during hemostasis.

This concept had to be modified when in 1977 Osterud and I presented unequivocal evidence that factor VIIa-tissue factor complexes could also activate factor IX.[10] The reduced sodium dodecylsulfate-polyacrylamide gels shown in Figure 7 illustrate part of the evidence. They show that in a reaction mixture containing tissue factor, factor VII, and calcium ions, the large, single-chain native molecule is cleaved to

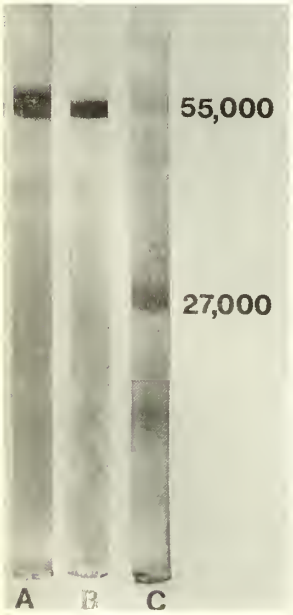

Figure 7.—Reduced sodium dodecylsulfate polyacrylamide gel electrophoresis of factor IX is shown. Single-chain native factor IX is shown in gels A and B, which were made after incubating factor IX in control incubation mixtures containing tissue factor and factor VII without calcium ions (gel A) or tissue factor and calcium ions without factor VII (gel B). Gel C was made after the incubation of factor IX in an incubation mixture containing tissue factor, factor VII, and calcium ions. It shows replacement of the protein band of native factor IX (molecular weight 55,000) by a protein band corresponding to the heavy chain of two-chain activated factor IX (molecular weight 27,000) and a weak protein band corresponding to the light chain of activated factor IX (from Osterud and Rapaport[10]).

yield the heavy chain and the poorly staining light chain of two-chain activated factor IX.

At first, some doubted the importance of our observation. After all, it had been known since 1935 that the prothrombin time test is normal in patients with hemophilia, which means that the direct VIIa-tissue factor activation of factor X that occurs in this test bypasses any delay imposed by the inability of a supplemental VIIa-tissue factor activation of factor IX to augment the activation of factor X. But hemostasis is initiated physiologically not by the high concentration of tissue factor used in the prothrombin time test but by the exposure of blood to a limited number of tissue factor sites on the surface membrane of cells. Much biochemical evidence now buttresses clinical observations that suggest that the VIIa-tissue factor activation of factor IX plays an important role in triggering hemostasis after tissue injury. I will not discuss the biochemical evidence but will summarize the clinical evidence.

As mentioned, the two ways to initiate blood coagulation are to expose blood to tissue factor and to a negatively charged surface. The latter begins the activation of factor XII and initiates the contact activation reactions (Figure 2, upper right) that lead to the activation of factor XI. Much is now known about these reactions, but they do not appear to be involved in the initiation of blood coagulation during hemostasis, since patients or indeed whole animal species lacking one or another of the factors do not bleed abnormally.

Persons lacking factor XI, however, do have an unusual bleeding disorder. They experience little, often no, excess bleeding into tissues after trauma, but they have a substantial risk for a persistent postoperative oozing of blood from open surfaces in areas of high fibrinolytic activity. This must mean that a mechanism independent of the contact activation reactions exists to activate factor XI during hemostasis. Recent data that thrombin and XIa can autocatalytically activate purified factor XI in vitro in the presence of negatively charged surfaces such as dextran sulfate, sulfatides, and heparin may provide a clue to such a mechanism.

Nevertheless, clinical experience makes clear that the primary event triggering the formation of a fibrin clot after tissue injury is not the generation of factor XIa but the exposure of the blood to tissue factor. As shown in Figure 2, during hemostasis factor IX can be activated in only two ways: by XIa and by VIIa-tissue factor complexes. If activation by XIa were the primary mechanism, then factor XI deficiency, like factor IX deficiency, should be a severe hemorrhagic disorder. Yet, patients with only traces of measurable plasma factor XI activity withstand the traumatic events of unrestricted daily living with minimal if any abnormal musculoskeletal bleeding. Indeed, the first patient I ever studied who had factor XI deficiency had played on his high school football team.

In contrast, patients with only traces of measurable plasma factor IX activity, that is, patients with severe hemophilia B, may have devastating musculoskeletal hemorrhages from trauma so trivial that the hemorrhage is considered spontaneous. Furthermore, patients with the rare severe hereditary factor VII deficiency and essentially no measurable plasma factor VII activity, like patients with severe hemophilia, also experience life-threatening bleeding.

Tissue Factor-Dependent Pathway of Blood Coagulation

Investigators in hemostasis research generally agree that the binding of factor VII to tissue factor expressed on cells

normally separated by an endothelial cell barrier from the circulating blood initiates blood coagulation after tissue injury. There are five points to be made about the early reactions of tissue factor-dependent blood coagulation (Figures 2 and 8). The first is that native factor VII is converted into the active enzyme, VIIa, only after factor VII is bound to tissue factor. This binding makes it possible for trace concentrations of proteolytic enzymes, particularly Xa, to catalyze the cleavage of the single peptide bond that converts the native zymogen into an active serine protease. The second point is that VIIa, once formed, cannot function as a physiologic enzyme in hemostasis unless it is bound to its cofactor, tissue factor. The third point is to repeat that VIIa-tissue factor complexes must activate two substrates, factor X and factor IX, during normal hemostasis. The fourth point is that factor X must also be activated by two mechanisms for normal hemostasis. These are a direct activation by VIIa-tissue factor and an indirect activation by a IXa-VIIIa-phospholipid complex. The severe bleeding of hemophilia attests to the crucial importance of this indirect activation mechanism.

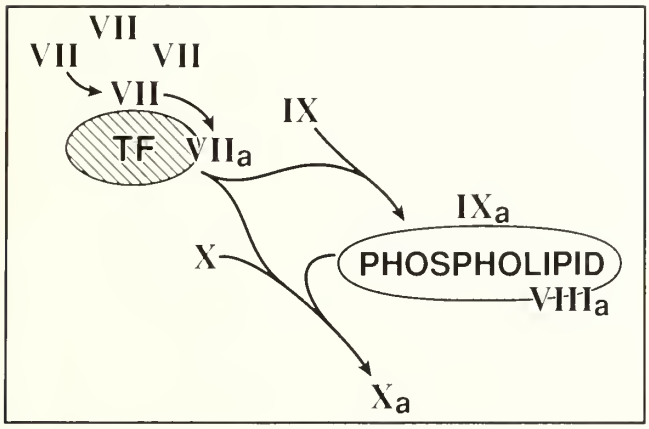

Figure 8.—The diagram shows why inhibiting the catalytic activity of VIIa-tissue factor (TF) would impair both the direct and indirect mechanism for activating factor X.

The fifth and final point is that the need to supplement the direct VIIa-tissue factor activation of factor X with an indirect IXa-VIIIa-phospholipid activation of factor X (Figure 8) stems from the inhibition of the direct activation of factor X as hemostasis proceeds. This results from a two-step inhibitory reaction involving an inhibitor, first described in 1957 by Hjort,[11] that my colleagues and I reported some 27 years later requires for its physiologic function the presence of factor X.[12]

There are other reactions schematically summarized in Figure 2. A point to note is that Xa, once formed, is the sole known physiologic enzyme capable of activating prothrombin. Factor Xa, however, cannot activate prothrombin efficiently by itself but only as part of a complex, referred to as prothrombinase, that is made up of Xa and its cofactors Va and anionic phospholipid. The surface membrane of activated platelets or other cells perturbed at a site of tissue injury—such as endothelial cells, fibroblasts—or vesicles from the surface membrane provide the anionic phospholipid needed for the formation of the prothrombinase complex and also of the IXa-VIIIa-phospholipid complex mentioned earlier.

It is also important to note key backactivation reactions: the activation of factor VII bound to tissue factor by Xa, and the activation of factors VIII and V by peptide bond cleavages catalyzed by thrombin. Factor Xa, with anionic phospholipid as a cofactor, can also catalyze activating cleavages in factor VIII and factor V, but cannot substitute for an initial proteolysis of factor VIII by thrombin. Factor VIII circulates in blood in a complex with von Willebrand factor, and only thrombin can catalyze an additional essential peptide bond cleavage that separates von Willebrand factor from factor VIII. This makes available a binding site on factor VIII for phospholipid that is required for VIIIa to function physiologically in a IXa-VIIIa-anionic phospholipid complex.

As mentioned earlier, blood coagulation involves a sequence of amplifying reactions. The initial proenzyme of the tissue factor-dependent reaction series, factor VII, has a plasma concentration of 10 nmol per liter, whereas the final proenzyme, prothrombin, has a 200-fold higher plasma concentration. One should also be aware of the remarkably low plasma concentration of 0.1 nmol per liter of the cofactor, factor VIII, which may well provide a clue to why the hemophilias are such severe bleeding disorders.

Regulation of the Activity of the Enzyme-Cofactor Complexes of Blood Coagulation

The three enzyme-cofactor complexes that form during blood coagulation in vivo localize the reactions leading to the generation of thrombin to the surface membrane of cells or to vesicles released from their surface membrane. Once thrombin is formed, it can then diffuse from these surfaces into surrounding plasma or interstitial fluid. As already mentioned, the enzyme-cofactor complexes are the VIIa-tissue factor complex that activates factors IX and X, the IXa-VIIIa-phospholipid complex that also activates factor X, and the Xa-Va-phospholipid complex that activates thrombin.

The catalytic activity of these complexes must be regulated during hemostasis. The components of the IXa-VIIIa-phospholipid and the Xa-Va-phospholipid complexes are neutralized separately. The enzymes IXa and Xa and also thrombin are inhibited by the serine protease inhibitor formerly called antithrombin III and now usually just antithrombin. It was known since 1892 that the activity of the thrombin generated when blood clotted progressively disappeared from the serum. But it was not until 1965, when Egeberg described a family in which nine members over three generations had had episodes of deep venous thrombosis associated with a reduced plasma level of the progressive antithrombin activity of plasma that we had clinical evidence of the importance of antithrombin as a natural anticoagulant.[13] Many subsequent studies of other families have confirmed that heterozygosity for antithrombin deficiency, which yields plasma levels in the 40% to 60% range of normal, carries with it a substantially increased risk for venous thrombotic disease. Homozygosity for antithrombin deficiency is lethal in utero.

The cofactors VIIIa and Va are inhibited by one of the vitamin K-dependent hemostatic factors, activated protein C. These hemostatic factors all have a number of glutamic acid residues in the aminoterminal segment of the molecule that possess an extracarboxyl group in the γ-position. This occurs in a posttranscriptional reaction that requires the participation of vitamin K. The extracarboxyl group on these glutamic acid residues allows the molecule to bind calcium ions properly and so to function effectively in hemostasis.

We had known since the mid-1950s that there were four

procoagulant vitamin K-dependent proteins: prothrombin, factor VII, factor IX, and factor X. In the 1970s the biochemists surprised everyone with the identification of three additional vitamin K-dependent plasma proteins. Two were found to be blood-clotting factors but to have anticoagulant functions. One was the serine protease proenzyme, protein C. The other was protein S, a molecule that has γ-carboxyglutamic residues in its aminoterminal segment but no serine protease catalytic domain and that functions as a nonenzymatic cofactor for activated protein C.

When thrombin is formed intravascularly, it can bind to a binding site on the luminal surface membrane of vascular endothelial cells called thrombomodulin. After its binding to thrombomodulin, thrombin acquires the ability to activate protein C. Activated protein C, with protein S and anionic phospholipid as cofactors, can then catalyze proteolytic cleavages in factors VIIIa and Va that destroy their cofactor functions.

Protein C with its cofactor protein S functions as another essential natural anticoagulant system. In 1981 Griffin and colleagues provided the first evidence that a reduced level of plasma protein C is associated with an increased risk for venous thrombosis.[14] Today it is generally recognized that heterozygotes for either protein C deficiency or protein S deficiency have an increased risk for thrombotic disease, primarily venous thrombosis. In 1984 Seligsohn and associates provided convincing genetic evidence that a fulminant thrombotic disorder of newborns, previously called neonatal purpura fulminans and fatal within hours or days of birth, was an expression of homozygous protein C deficiency.[15]

About ten years ago, to learn what the intravascular half-disappearance time of protein C was, I took a single 40-mg dose of warfarin and measured the rate of fall of my plasma protein C antigen level (Figure 9).[16] It was a little more than five hours, which is essentially the same as that for factor VII and much faster than the intravascular half-disappearance time of factor X, which I also measured, and of prothrombin, which was known to be even longer than the half-disappearance time of factor X. Therefore, in a patient who is heterozygotic for protein C with a plasma protein C level of only 40% to 50% of normal, warfarin therapy must be started cautiously to prevent the protein C level from falling to a very low level before the levels of factor X and prothrombin have time to fall into the antithrombotic range. Otherwise, the onset of hemorrhagic necrosis of skin and underlying tissues—the purpura fulminans-like lesion of warfarin-induced skin necrosis—may be triggered.[17]

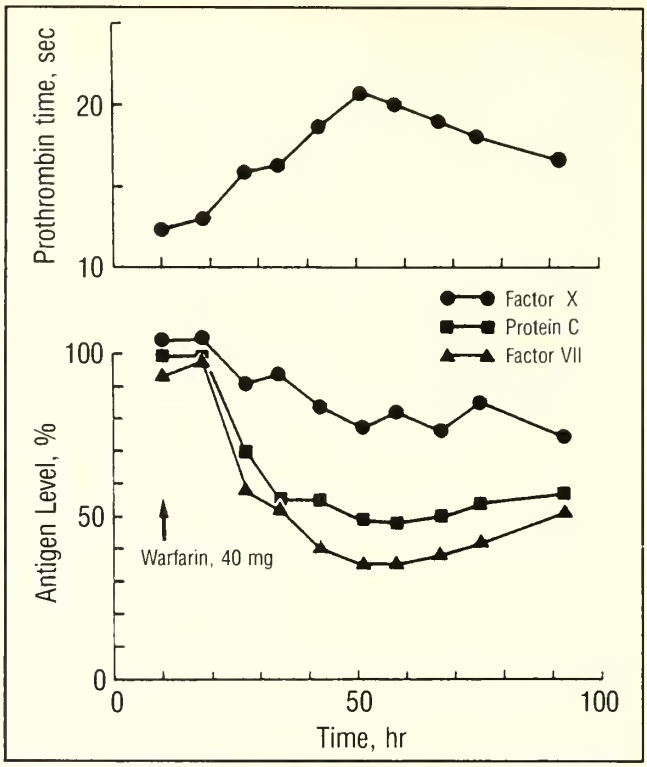

Figure 9.—The graphs show protein C, factor X, and factor VII antigen levels in serial plasma specimens after a single oral 40-mg dose of warfarin sodium. The relationship between the antigen levels and the prothrombin time is also shown (from Epstein et al[16]).

Tissue Factor Pathway Inhibitor

I now want to discuss how the catalytic activity of the first enzyme-cofactor complex formed during tissue factor-dependent coagulation, the VIIa-tissue factor complex, is neutralized. Its neutralization differs fundamentally from the IXa-VIIIa- and Xa-Va-phospholipid complexes, whose enzymatic and cofactor components are more readily inhibited before they form complexes. The components of the factor VIIa-tissue factor complex cannot be inhibited separately. Moreover, the catalytic activity of the complex cannot be neutralized under physiologic conditions until the activated product of one of its substrates, Xa, is also present.

The Kunitz-type protease inhibitor neutralizing the complex has had two former names: extrinsic pathway inhibitor and lipoprotein-associated inhibitor. To avoid the continuing confusion of a dual nomenclature, a new name has recently been suggested by the Scientific Subcommittee of the International Society of Thrombosis and Haemostasis, that of tissue factor pathway inhibitor (TFPI). The tissue factor pathway inhibitor is a molecule with three Kunitz domains. Factor Xa binds to a reactive center arginine in the second domain to give rise to a Xa-TFPI complex. Then VIIa, when part of a VIIa-tissue factor complex but not otherwise, can bind to a reactive center lysine in the first Kunitz domain.

Figure 10 shows the sequence of events that leads to the inhibition of VIIa-tissue factor catalytic activity following the initiation of tissue factor-dependent blood coagulation

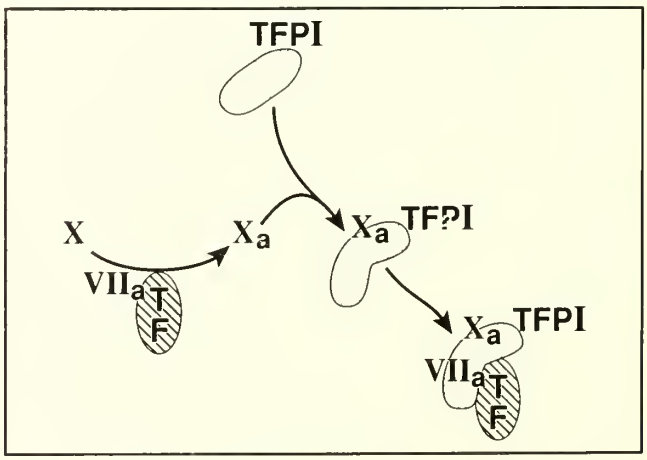

Figure 10.—A schematic representation is shown of how the generation of factor X by the catalytic activity of VIIa-tissue factor (TF) complexes may initiate a two-step reaction in which a Xa-tissue factor pathway inhibitor (TFPI) complex inhibits further VIIa-TF catalytic activity.

during hemostasis. Factor VIIa-tissue factor complexes begin the activation of factor X. As Xa accumulates it can interact with TFPI to form Xa-TFPI complexes, which can then form a quaternary Xa-TFPI-VIIa-tissue factor complex with inhibited catalytic activity.

The bleeding of hemophilia can be accounted for by the physiologic functioning of this inhibitory mechanism. Its turning off of the direct VIIa-tissue factor activation of factor X leaves the continuing activation of factor X dependent on factor IXa-VIIIa-phospholipid complexes. This hypothesis makes good sense, but the difficult experiments to test it in a hemophilic animal immunodepleted of TFPI have yet to be done. Moreover, there is a problem to be solved, which is illustrated in Figure 8. If TFPI turns off the catalytic activity of the VIIa-tissue factor complex, then how is factor IXa activity maintained at a level adequate to keep the indirect activation of factor X going? Some may postulate that this results from a continuing activation of factor IX by XIa. If so, then why is factor XI deficiency not a more severe bleeding disorder, a third form of hemophilia?

Much remains to be learned about the physiologic function of TFPI. Its plasma concentration is low, 2.5 nmol per liter, which is a fourth that of factor VII and 1/1,000 that of antithrombin. But in addition to the plasma pool of TFPI, it is now known that a substantially larger pool of TFPI exists bound to glycosaminoglycans on the luminal surface of vascular endothelium. This TFPI, analogous to other similarly bound materials such as lipoprotein lipase, is released into the circulating blood after a bolus injection of heparin. There have been two large studies looking without success for patients with thrombotic disease and low plasma levels of TFPI. As yet, however, no systematic studies have been done of the size of the vascular endothelial surface pool of TFPI and of physiologic variables that might influence it. This information is obviously needed before a meaningful search for patients with thrombotic disease due to a reduced physiologic function of TFPI can be carried out.

Acquired Disorders of Blood Coagulation

It helps to remember, when attempting to account for puzzling clotting test results in a difficult patient, that there are only four known common causes of acquired abnormalities of blood coagulation: vitamin K deficiency, hepatocellular disease, antibodies that react with clotting factors, and disseminated intravascular coagulation (DIC) usually with secondary fibrinolysis. I will comment only about antibodies that react with clotting factors and about DIC.

Antibodies can deplete blood of its clotting activity by two mechanisms. An antibody may have neutralizing activity demonstrable in vitro by assaying for the clotting activity persisting after incubating normal plasma, as a source of the clotting factor, with the patient's plasma. Such an antibody is easy to recognize. For example, when a source of factor VIII is added in a test tube to the plasma of a hemophilic patient in whom a neutralizing antibody to factor VIII has developed, the added factor VIII activity rapidly disappears from the mixture. An antibody may also deplete the blood of clotting activity through the accelerated mononuclear phagocytic clearance of immune complexes of antibody and clotting factor. If the antibody happens not to have neutralizing activity readily recognizable in vitro on mixing the patient's plasma with normal plasma, then its presence may not be easy to recognize. Its identification requires a demonstration of a binding of the antibody to the clotting factor, a search for more subtle neutralizing activity by methods requiring the use of purified reagents and assay systems available only in coagulation research laboratories, or both techniques.

The antibodies causing acute hypoprothrombinemia in patients with a lupus anticoagulant are an example of this second type of antibody. When normal plasma as a source of prothrombin is incubated with the prothrombin-deficient plasma of such a patient, the prothrombin activity of the normal plasma persists. A specific assay for prothrombin performed on the mixture yields the same value for prothrombin activity as is found in a mixture of normal plasma with a control buffer. If, however, a crossed immunoelectrophoresis is performed on the mixture of the patient's plasma and the normal plasma, then a pronounced distortion and lag can be shown of the prothrombin precipitin arc as evidence of the binding to prothrombin of the antiprothrombin antibody in the patient's plasma (Figure 11).[18]

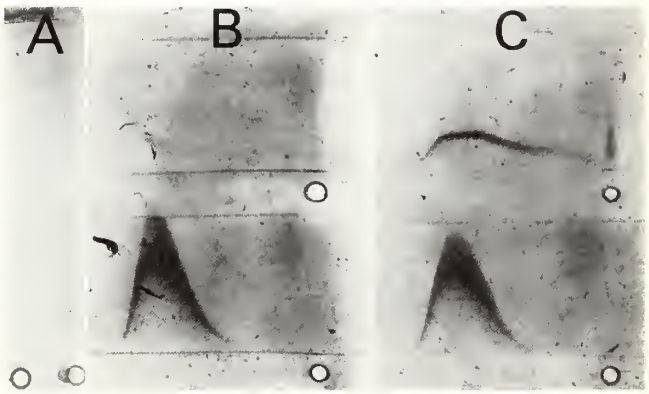

Figure 11.—A crossed immunoelectrophoresis (CIE) has been done that shows antiprothrombin antibodies capable of binding prothrombin in the plasma of a patient with the lupus anticoagulant and severe acquired hypoprothrombinemia. **A,** The absence of prothrombin in the patient's plasma is shown by the absence of a prothrombin antigen rocket on electroimmunoassay. **B,** The absence of a prothrombin arc is shown on CIE of the patient's plasma (top well); a prothrombin arc of normal pooled plasma is shown in the bottom well. **C,** The broad, low prothrombin arc, with an anodal shoulder and a peak persisting at the origin, is seen on CIE of a 1:1 mixture of patient's plasma and normal plasma (top well); a control plasma is shown in the bottom well (from Fleck et al[18]).

There is another point worth mentioning about antibodies to clotting factors. Although antibodies reacting with hemostatic factors are usually autoantibodies, sometimes they arise from immunization. A well-known example of this is the antibodies to factor VIII arising in some patients with hemophilia A after factor VIII replacement therapy because the patient's immune system views the infused factor VIII as a foreign protein. Antibodies arising after commercial bovine thrombin is applied topically during a surgical procedure is another, less well-known, recently recognized example. Bovine thrombin preparations contain small amounts of contaminating bovine factor V that may trigger the synthesis of antibodies to bovine factor V. Occasionally these antibodies may cross-react in a high enough titer with human factor V to deplete a patient's blood of factor V activity. There are two clues to this mechanism for a postoperative factor V anticoagulant. The first is that the patient's thrombin time with the standard bovine thrombin used for the test in the clinical laboratory will be long because the patient has also made antibodies against bovine thrombin. The second is that the antibody titer against factor V in a barium-adsorbed bo-

vine plasma reagent will substantially exceed the antibody titer against factor V in a barium-adsorbed human plasma reagent.

Disseminated Intravascular Coagulation

Clotting reactions are normally dormant in the circulating blood because the circulating blood does not come into contact with the tissue factor needed to trigger the reactions. As immunostaining studies of the distribution of tissue factor

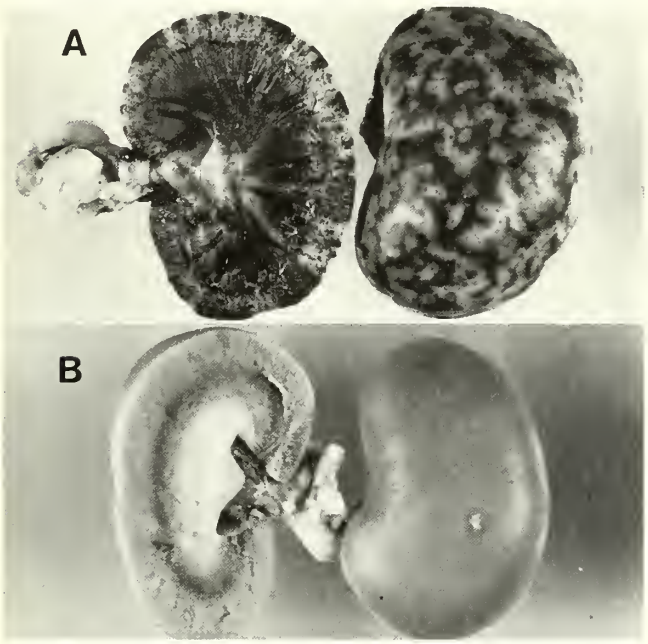

Figure 12.—**A,** Hemorrhagic necrosis of the kidney (generalized Shwartzman reaction) occurred in a rabbit immunodepleted of tissue factor pathway inhibitor (TFPI) with goat anti-rabbit TFPI Fab before being given an intravenous injection of gram-negative endotoxin. **B,** A normal kidney is shown from a control rabbit given non-immune goat immunoglobulin G before the intravenous injection of the same dose of gram-negative endotoxin (from Sandset et al[19]).

apoprotein have demonstrated, an endothelial cell barrier separates the blood from cells staining for tissue factor apoprotein located in the outer layers of blood vessel walls. Two cells to which the circulating blood is exposed, however, the endothelial cell and the monocyte, can express surface tissue factor activity after stimulation by a variety of materials, such as thrombin, endotoxin, and such cytokines as interleukin 1 and tumor necrosis factor. If such stimulation and resultant expression of surface membrane tissue factor activity is within certain limits, as, for example, when someone becomes ill with the infections and inflammatory disorders of normal living, then the normal functioning of TFPI can prevent the catalytic activity of VIIa-tissue factor complexes that may form intravascularly from inducing notable intravascular coagulation.

The evidence for this comes from extrapolating to humans experimental results my colleagues and I obtained from infusing a low concentration of reconstituted, purified tissue factor or of endotoxin into normal rabbits and into rabbits immunodepleted of TFPI. In our experiments with endotoxin, we prepared rabbits with cortisone to undergo DIC after a single intravenous injection of endotoxin. We chose a dose of endotoxin so low, however, that it failed to induce DIC in control rabbits with a normal plasma level of TFPI. When the same dose of endotoxin was given to rabbits immunodepleted of TFPI, fibrinogen levels fell because of DIC and the animals experienced a generalized Shwartzman reaction—gross renal cortical necrosis resulting from fibrin deposition in the glomerular capillary beds (Figure 12).[19]

Tissue factor pathway inhibitor, however, can protect against only a limited exposure of the circulating blood to tissue factor. The evidence is now irrefutable that tissue factor triggers the DIC that occurs in patients with overwhelming gram-negative endotoxemia. Tissue factor also may trigger intravascular coagulation in patients with certain types of malignant neoplasms in which tumor cells constitutively expressing surface membrane tissue factor or vesicles shed from such tumor cell membranes gain access to the circulating blood. We have learned that DIC continues in most such patients not because plasma TFPI levels are depleted but because the formation of new VIIa-tissue factor complexes exceeds the ability of a normal or even elevated level of plasma TFPI to suppress their catalytic activity.

An example of this is shown in Figure 13, which is a plot of data from a patient who underwent a thoracic operation for a gunshot wound.[20] A laceration of the myocardium was sutured and a damaged lobe of the lung removed. The patient did reasonably well for the first several days. The fibrinogen level rose as part of an acute-phase response. On the day that he was extubated, however, his condition worsened. Fever developed, his fibrinogen level fell, and he became acutely

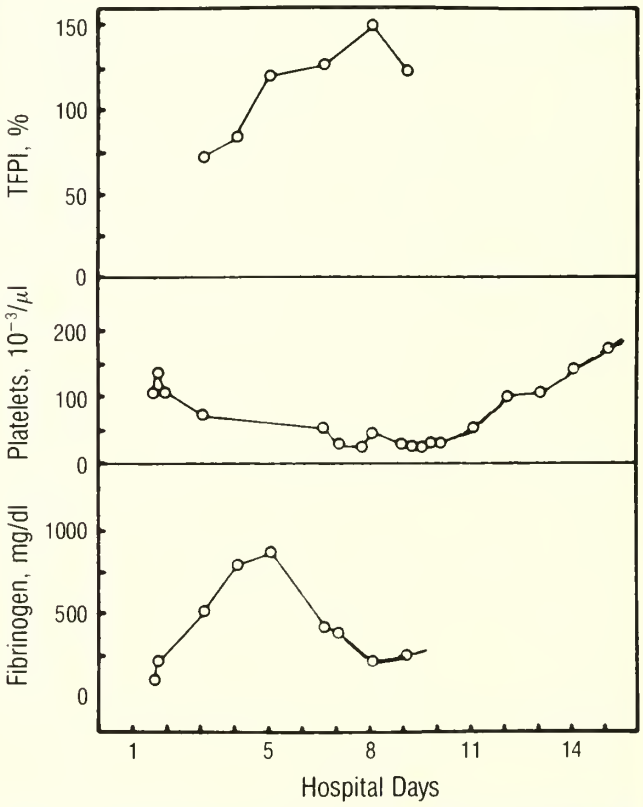

Figure 13.—Serial values are shown for tissue factor pathway inhibitor (TFPI), platelets, and fibrinogen from a patient in whom disseminated intravascular coagulation developed secondary to a thoracic abscess caused by a gram-negative bacillus. The patient underwent a thoracic operation for a gunshot wound on day 1. The increase in fibrinogen through day 5 reflected an acute-phase response to trauma, surgery, and infection. The subsequent decrease in fibrinogen beginning on day 5 resulted from the consumption of fibrinogen in intravascular coagulation triggered by gram-negative endotoxemia. Note that the plasma level of TFPI continued to rise while the plasma level of fibrinogen was falling (from Warr et al[20]).

and, unfortunately, permanently anuric, presumably due to a generalized Shwartzman reaction. After some searching, the reason for this turn of events was found: a mediastinal abscess caused by infection with a gram-negative organism. As seen in Figure 13, the DIC induced by the resultant gram-negative endotoxemia continued in this patient despite a rising plasma level of TFPI.

Trousseau's Syndrome

The administration of heparin can suppress DIC in patients with gram-negative sepsis and in those with malignant neoplasms. I had always attributed this to heparin's potentiation of the inactivation of thrombin, factor Xa, and factor IXa by antithrombin, and this may be how it exerts its principal anticoagulant effect. Nevertheless, I had been puzzled as to why anticoagulation with heparin suppresses—whereas anticoagulation with warfarin does not suppress—the chronic, low-grade DIC and thrombotic episodes of Trousseau's syndrome, a syndrome in which recurrent or migratory venous thromboses, arterial emboli due to nonbacterial thrombotic endocarditis, or both, develop in patients with recognized or occult cancer. Considerable evidence now supports the hypothesis that a continuing entrance into the circulation of tissue factor from malignant cells is responsible for the manifestations of Trousseau's syndrome in most patients. Therefore, it is of considerable interest that there are now data from two laboratories to suggest that heparin's anticoagulant activity may also stem from its ability to potentiate the anticoagulant activity of TFPI, the inhibitor responsible for neutralizing VIIa-tissue factor coagulant activity.

Future Challenges

I have tried to review present concepts of blood coagulation and its alterations in certain disease states from a historical perspective and with emphasis on how past clinical observations have helped us to understand basic mechanisms. What of the future? What are the clinical disorders begging for understanding that could provide basic new information about the regulation of hemostasis? My list begins with two disorders: thrombotic thrombocytopenic purpura and thrombosis associated with antiphospholipid antibodies. What is the material in the large quantities of plasma given after plasmapheresis to patients with thrombotic thrombocytopenic purpura that stops the formation of the bland platelet-fibrin thrombi which are the hallmark of this disorder? By what mechanism or mechanisms do antiphospholipid antibodies increase a patient's risk for thrombosis? Finding answers to these questions is a major challenge for today's investigator of the regulation of hemostasis whose research goals arise from the responsibilities of a physician caring for patients.

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Conferences and Reviews

Interventional Neuroradiology

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A wide variety of diseases affecting the central nervous system and head and neck can be treated using interventional neuroradiologic techniques. These new treatments have depended on advances in radiologic imaging, catheter technology, and the development of new embolic agents. These procedures may be an adjunct to other therapy, palliative or curative. Diseases for which interventional neuroradiologic techniques have been major advances in treatment include cerebral aneurysms, vasospasm after subarachnoid hemorrhage, cerebral arteriovenous malformations, dural arteriovenous fistulas, dural sinus thrombosis, atherosclerosis, scalp arteriovenous fistulas, carotid-cavernous fistulas, and stroke. This field is rapidly evolving as advances are made in catheter technology and new embolic agents are developed.

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The occlusion of blood vessels by an endovascular approach was first described in 1930 for the treatment of a traumatic arteriovenous fistula.[1] This approach to lesions in the central nervous system was not developed until more recently because of limitations in catheter technology and imaging. The first endovascular approach to treating a cerebral arteriovenous malformation was described in 1960.[2] As advances occurred in radiologic imaging, the field of interventional neuroradiology developed.[3] Endovascular therapy became a more routine part of radiology in the 1970s, with the development of better radiologic imaging, catheters, and guide wires.[3] The treatment of cerebral arteriovenous malformations became a prime motive for developing interventional neuroradiology because of difficulty with the surgical treatment of this disease.

Methods

Imaging

Advances in neurointerventional radiology have depended in large part on imaging technology. Subtraction angiography allows the visualization of small vessels without the interference of overlapping bony structures.[4] Most of the work done currently uses digital angiography rather than direct imaging of x-rays on photographic film.[5] Television cameras can detect small differences in radiation exposure more reliably than conventional photographic plates. The digital memory and electronic subtraction produce real-time images that can be subtracted instantly.

The technique of "road mapping" adds greatly to the ease and efficacy of endovascular surgery. Road mapping involves projecting a subtracted vascular pathway, such that the blood vessel is continuously displayed, much as on a road map, under live fluoroscopy without imaging the bones. This technique allows the course of a moving catheter to be followed through a blood vessel. The neurosurgeon may direct a catheter into a selected pedicle supplying an arteriovenous malformation or a balloon into an aneurysm, for example, without the image being obstructed by overlying bone.

Embolic Agents

A wide variety of agents have been used to produce vascular occlusion for the treatment of vascular lesions. These agents can be grouped into those that cause proximal occlusion of vessels supplying a lesion and those that penetrate into the nidus of a lesion.

Proximal occlusion of vessels is useful in treating lesions before surgical therapy. This blockage can reduce the size and pressure within the nidus and diminish the number of feeding pedicles, allowing for an easier operation. The disadvantage to proximal occlusion is that it generally cannot be used as the sole form of therapy because there will be enlargement of collateral feeders. Proximal occlusion also prevents a later use of this pedicle if more selective catheterization and embolization are planned for the future.

The proximal aspect of vessels can be occluded with detachable balloons and platinum coils.[6,7] The use of balloons allows neurologic testing before permanent occlusion. In the largest series of balloon occlusions in preparation for the surgical treatment of cerebral arteriovenous malformations, 36 feeders were occluded in 31 patients.[6] In only two patients did stroke occur as a result of these occlusions, and the surgical procedure was judged to be considerably less difficult. Vessels can also be occluded using platinum coils. These coils do not interfere with magnetic resonance imaging and are small enough to be delivered to pedicles close to the malformation.

Agents that penetrate into the small vessels composing the nidus of a lesion include cyanoacrylates, polyvinyl alcohol particles, ethanol, and microfibrillar collagen. The most commonly used agents are cyanoacrylates and polyvinyl alcohol. All of these agents are able to cause proximal vessel occlusion.

Most large series of patients with cerebral arteriovenous malformations treated by embolization show the results using bucrylate (isobutyl 2-cyanoacrylate).[8] Because of concerns over the carcinogenicity of this agent, *N*-butyl-2-cyanoacrylate has been substituted.[9] Although generally thought to be a permanent occlusive agent, there can be dissolution and resorption of the glue over a period of months.[10,11]

Polyvinyl alcohol (Contour, Interventional Therapeutics Corporation, South San Francisco, Calif) is the particulate agent most frequently used in the treatment of many lesions.[12-14] Particle size is chosen by estimating the size of

From the Charles Dotter Institute of Interventional Therapy, Division of Neurosurgery, Oregon Health Sciences University, Portland.

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shunts within the malformation. Occlusion is best obtained if the particles lodge in the nidus rather than proximally.

A variety of agents are under investigation as embolic agents.[15-18] The use of silk suture is effective in closing large fistulous connections within arteriovenous malformations.[15] Ethylene vinyl alcohol copolymer and metrizamide dissolved in dimethylsulfoxide forms an ethylene vinyl alcohol copolymer sponge that obstructs both the feeding artery and nidus.[18] This agent may be better than glues because it stays liquid and will not hold the catheter in the blood vessel, despite its ability to occlude the nidus of a lesion. Ethyl alcohol causes blood vessels to occlude when administered in sufficient concentration.[16] It may be useful in obliterating the nidus of a lesion and is relatively easy to administer.

Techniques

Superselective Catheterization for Analysis of Angioarchitecture and Flow

It is critical to obtain highly selective pictures of an artery before it is occluded.[19] This information is not necessarily apparent on global proximal artery images where the angioarchitecture of a lesion such as an arteriovenous malformation is rapidly obscured. Highly selective catheterization allows the anatomy of the lesion to be evaluated, with particular attention directed at finding aneurysms and evaluating normal vessels in the area. When combined with the high-speed acquisition of images, as many as 30 images per second, complete information on flow and aneurysms can be obtained. Information about flow through the lesion is critical in determining which embolic agents to use and for the proper preparation of the agents in terms of size of particles or polymerization times of liquid adhesives.[20] Data obtained from this superselective catheterization add greatly to the safety of the procedure.[19]

Using Provocative Testing Before Embolization

Before occluding a vessel that supplies a lesion, testing is done that may predict any functional loss from blocking that vessel. The selective administration of amobarbital into intracranial arteries before embolization has been used for more than ten years.[21-23] This test is a variation of the Wada and Rasmussen test, wherein amobarbital is introduced into the internal carotid artery to test for language function.[24] The test is generally considered to be reliable, although there may be false-positive or false-negative results. Overinjection may cause reflux into normal vessels, giving false-positive results.[23] Underinjection, or sumping of the drug into an arteriovenous malformation and bypassing normal branches, may lead to false-negative tests.

Amobarbital is typically used for the intracranial circulation but will not affect cranial nerve function. The use of lidocaine is more effective for testing cranial nerve function and sight.[25]

Neurologic Testing During Embolization

The neurologic examination of an awake patient is probably the most sensitive indicator of the effect of an embolization procedure. When the embolization is preceded by a full understanding of the vascular anatomy, provocative testing with amobarbital, and under constant neurologic monitoring, it is generally safe. Most of the reports with large numbers of patients note the importance of doing the procedures in awake patients while closely monitoring the clinical state, especially for cerebral arteriovenous malformations. The use of neuroleptic analgesia is generally advocated for these procedures to make them more tolerable for patients.[26]

At times it becomes necessary to do these procedures using a general anesthetic because the patients are moribund, uncooperative, or children. In these cases, electroencephalography, continuous recording of brain-stem acoustic responses, and somatosensory-evoked cortical potentials may be used for monitoring both hemispheric and brain-stem functions.[27]

Cerebrovascular Diseases Treated by Endovascular Techniques

Intracranial Aneurysms

The treatment of choice for most aneurysms is surgical clipping. Some aneurysms, because of their size or location, cannot be safely treated surgically. Some patients are judged too ill to undergo a surgical procedure requiring a general anesthetic or they may refuse to undergo one. The natural history of these previously untreatable aneurysms is dismal. Interventional neuroradiologic techniques have emerged as an alternative to surgical therapy for selected lesions.

The use of detachable balloons for the treatment of aneurysms allows treatment by occluding the parent vessel from which the aneurysm originates or, preferably, with preservation of the parent vessel by direct aneurysm occlusion.[28,29] A series of 84 patients in whom an aneurysm was treated while preserving the parent artery showed complete aneurysm obliteration in 65 (77%), with follow-up of 3 to 68 months (mean of 35.5 months) and subtotal occlusion in 19 (23%).[29] All of these cases were considered not amenable to surgical therapy, or the lesions had been explored and found to be unclippable. The complication rate, including fatal hemorrhages and all strokes, was 32%. The complications were much more frequent in patients with large aneurysms who had presented with hemorrhage and for which no surgical therapy could be given. Among 87 cases of cavernous carotid artery aneurysms, which generally have a more benign course than other intracranial aneurysms, the parent vessels were spared in 19 (22%) and occluded in 68 (78%).[28] Substantial complications consisting of nonfatal stroke occurred in only 4 (5%) of these patients, and there were no deaths. Among a series of 21 vertebrobasilar artery aneurysms that could not be treated surgically, vertebral artery occlusion was performed.[30] In this group there were good outcomes consisting of complete obliteration in 13 (62%), subtotal occlusion of the aneurysm in 6 (29%), death in 1 (5%), and failed treatment in 1 (5%). In another series of 16 patients with surgically untreatable, high-risk aneurysms, 12 patients (75%) had excellent results without neurologic complications.[31] There were 3 deaths (19%) related to the treatment and 1 death from rupture of a second untreated aneurysm. The patients from these reports would all be considered at high risk.

Complications unique to the endovascular approach may occur in the course of treating these lesions. As the lumen of the aneurysm thromboses in response to the embolic material placed within the aneurysm, some of the clot may enter the parent vessel and occlude it or embolize distal branches. If recognized early, this clot may be dissolved with intra-arterial administration of thrombolytic agents to prevent an ischemic stroke. There are cases where the aneurysm is partly thrombosed before treatment and the embolic agents,

balloons, or coils may migrate into the clot, resulting in the aneurysm lumen reforming. Retreatment may be necessary in such cases.

The technology of the endovascular treatment of intracranial aneurysms is rapidly changing. Although the complication rate has been high, it must be remembered that these lesions have no other treatment and a dismal natural history. Advances continue to be made in this form of therapy. The use of detachable platinum coils may completely change the way aneurysms are treated in the future.[32,33] This new technology has many advantages over balloons, and although still experimental, initial results are promising.

Angioplasty for Vasospasm

Intracranial arterial spasm occurs in about 30% of patients with aneurysmal subarachnoid hemorrhage, usually within 5 to 12 days of the hemorrhagic event.[34-38] Recognized as a serious complication, it increases the risk of cerebral infarction and contributes to the high morbidity and mortality associated with aneurysmal bleeding: less than 50% of patients survive, and only 36% of patients return to full employment.[34]

Cerebral vasospasm is a diffuse process, although there is a tendency for involvement of vessels in the circle of Willis.[34,39-42] The involvement of a particular vessel may extend over a long distance or be focal. The mechanisms that result in vasospasm are not clearly understood but may include vasoconstriction from endogenous agents released from subarachnoid blood,[40,43] intimal hyperplasia,[44-45] and muscular contraction producing anoxia in the wall of the vessel.[46-51]

Many pharmacologic agents have been evaluated to treat this condition, but none consistently reverse the clinical manifestations.[52] Medical therapies such as the use of calcium channel blockers, induced arterial hypertension, or expanded intravascular volume have also been advocated. These therapies are associated with complications, however, and their effectiveness remains to be adequately demonstrated.[53]

The use of transluminal angioplasty to treat vasospasm associated with aneurysmal subarachnoid hemorrhage was first described in 1984 and shown to reverse arterial spasm and restore cerebral perfusion in patients with aneurysmal subarachnoid bleeding.[54] In the first report, 33 patients with symptomatic vasospasm benefited from this procedure; they showed marked improvement in their neurologic condition accompanied by angiographic evidence of arterial widening, although details of the neurologic examinations were not given.[54] Since that first report, a new microballoon has been developed for the dilation of intracranial arterial spasm resulting from subarachnoid hemorrhage (Figure 1).[55] The balloon is composed of a silicon shell attached to a 2.0-F catheter. It inflates symmetrically and from the proximal end to the distal end. It generates a low pressure, less than 1 atm, so has a low risk of rupturing the vessel.

Using this new balloon, angioplasty reversed the neurologic deficits in 9 of 13 patients with symptomatic vasospasm after subarachnoid hemorrhage, in all of whom medical therapy had failed.[56] The four patients who had no improvement were in the Hunt and Hess grades 4 and 5 neurologic condition, which places them in a poor prognostic category.[57] In another series, eight of ten patients with symptomatic vasospasm improved after angioplasty.[58] Improvement in neurologic function has occurred even when the deficits have been long-standing, over 36 hours.[59]

The incidence of complications from angioplasty of intra-

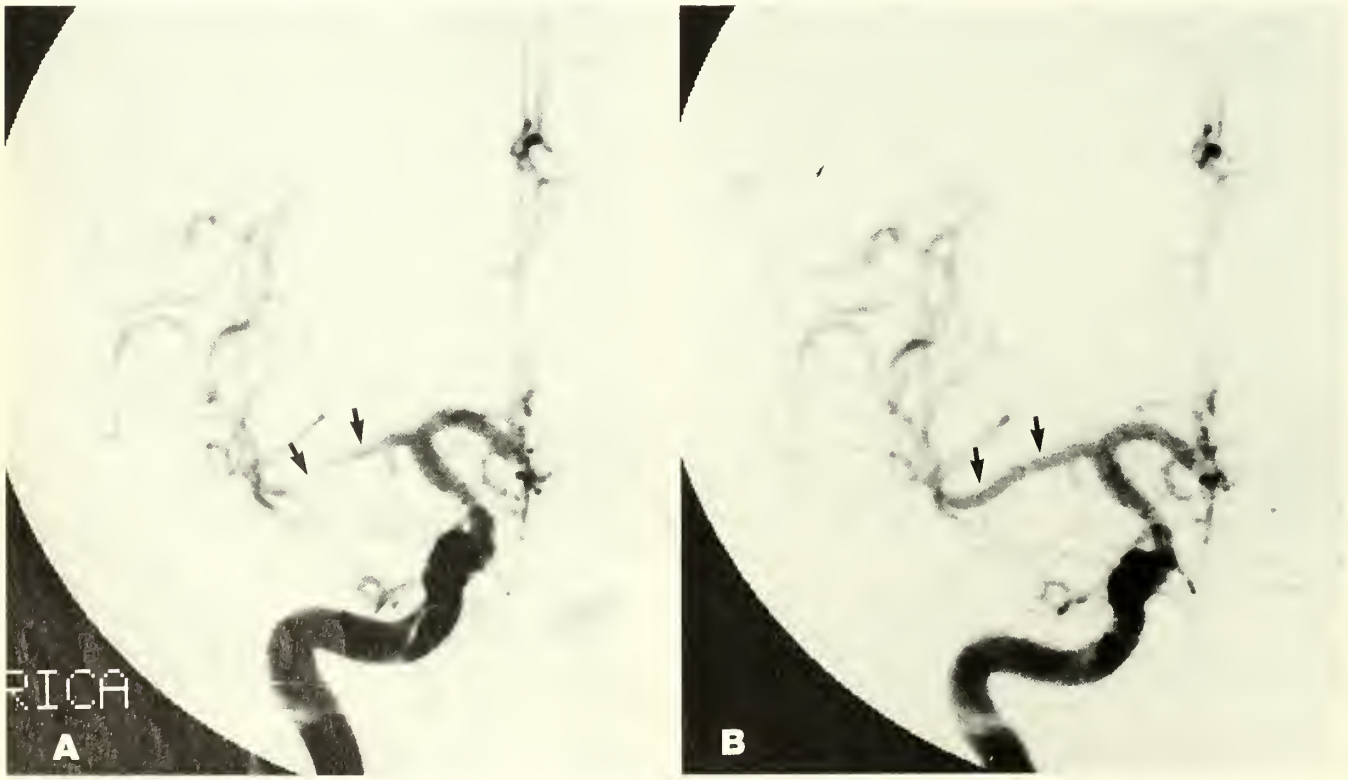

Figure 1.—A, Right internal carotid artery catheterization, frontal view, shows severe narrowing (arrows) of the middle cerebral artery resulting from an aneurysmal subarachnoid hemorrhage. B, The middle cerebral artery was dilated with silastic balloon (Interventional Therapeutics Corporation, South San Francisco), and the vessel lumen (arrows) is now normal with improved distal perfusion.

cranial vessels has been low. Among the two largest series of 23 patients, there were three complications that included hemorrhage from an unclipped aneurysm, middle cerebral artery occlusion, and hemorrhagic infarction, possibly caused by reperfusion of an infarcted area of the brain.[56,58] Fatal rupture of a vessel has also been described.[60] These complications can be reduced by not dilating blood vessels associated with unclipped aneurysms, not treating vascular territories with known infarction, and not overinflating the balloon.

The use of angioplasty to treat vasospasm after subarachnoid hemorrhage is a new therapy with the results unproven but encouraging. There are many issues surrounding this therapy that are unresolved, particularly the timing of therapy and the effect on small blood vessels and perfusion of the microcirculation.[56] In the acute stages of vasospasm, however, it has been shown that spastic vessels can be dilated and distal circulation improved.

Cerebral Arteriovenous Malformations

The endovascular treatment of cerebral arteriovenous malformations began as an alternative to surgical therapy in the 1960s.[3] At the time this form of therapy began, the surgical treatment of cerebral arteriovenous malformations was only occasionally successful in completely removing the lesion and usually was only done on small lesions in nonfunctional areas of the brain.[3] For cases with poor surgical results, Luessenhop and Spence described the first endovascular approach to treating an arteriovenous malformation.[2] At first, embolic agents were delivered to the malformations using flow patterns from proximal catheter locations. As catheter technology improved, it became possible to introduce embolic agents from catheters lodged in or adjacent to the malformation, thereby increasing safety and effectiveness.

The indications to treat an arteriovenous malformation are primarily related to the prevention of hemorrhage. Hemorrhage is one of the most common presentations of a cerebral arteriovenous malformation, with the frequency ranging from 30% to 86% in large series.[61-63] The mortality from the first hemorrhage is about 10% and morbidity at least 30%.[64] Once a hemorrhage has occurred, the risk of another hemorrhage within the first year is about 6%, and for subsequent years the risk of hemorrhage is about 3% to 4% a year with an annual mortality of 1%.[65,66] Among one of the largest series with long-term follow-up, 23% of patients died of hemorrhage from the malformation, and the presentation, whether hemorrhage, headache, seizures, or neurologic deficits, did not alter the ultimately poor prognosis for many of these lesions.[66]

The indications for therapy for a cerebral arteriovenous malformation include lesions that have bled to prevent rehemorrhage, uncontrolled headaches, progressive neurologic deficits, uncontrolled seizures, and a preoperative or preradiosurgical adjunct. In addition, patients with lesions with identified risk factors for hemorrhage, such as venous occlusive disease and aneurysms, should also be considered for treatment.

The methods used in treating an arteriovenous malformation are complex. Highly selective angiography is used to define the vascular supply to the lesion and thereby avoid occluding normal vessels. Before occluding a vessel, functional testing can be done with amobarbitol to evaluate whether or not any functional brain is supplied by the vessels and to reposition the catheter as necessary to avoid those normal branches.[21-24] Generally embolizations are performed with the patient awake so that constant neurologic monitoring can be done. A wide variety of embolic agents are available for producing vascular occlusion, including balloons, wire coils, liquid adhesives, and particles. The decision to use one agent over another is largely determined by the experience of the neurosurgeon.

The results of embolization of cerebral arteriovenous malformations have been the subject of 14 recent series, each reporting at least 15 patients.[6,7,19,21,22,67-75] These reports are retrospective studies of the results of embolizations. They do not address a uniform set of questions, although they do give data concerning the results of embolization.

The primary benefit of embolization is a preoperative reduction in blood flow (Figure 2). Embolization can change a vascular lesion into an avascular tangle of thrombosed vessels, thereby greatly reducing the risk of surgical excision. The surgical removal is substantially easier and faster, requiring removal of less normal brain adjacent to the lesion. It is rare, however, that an arteriovenous malformation can be cured by endovascular approaches because of the recanalization of occluded vessels.

The prevention of hemorrhage has not been clearly shown to be a result of embolization. The recognition of risk factors for hemorrhage, however, such as aneurysms within the nidus of an arteriovenous malformation, and occlusion of that vessel would appear to offer some protection against further hemorrhage. In four of these large series, there were no recurrent hemorrhages among 78% to 100% of patients treated who had originally presented with hemorrhage.[21,69,71,75] Resolution or notable lessening of headaches after embolization was noted in 50% to 71% of patients treated.[21,68,75] Neurologic dysfunction due to these lesions may improve after embolization. In three of these large series where neurologic deficits were evaluated, improvement occurred in 50% to 59%.[68,70,75] Reduction in seizure frequency varies after embolization. A resolution or reduction was noted in 7% to 61% of treated patients.[21,68,75]

Complications from embolization may include transient neurologic deficits, strokes, and hemorrhage. Transient neurologic deficits occurred in 2.5% to 31% of patients. The highest rates were seen when liquid adhesives were used as the embolic agent. Strokes occurred in 1.6% to 20% of patients, and again the highest risk was associated with the use of liquid adhesives rather than particulate agents.* Among these reports including 503 patients, there were 22 hemorrhages for an overall risk of 4.3%. When a hemorrhage did occur, 31.8% were fatal, underscoring the seriousness of this complication. This poor outcome from hemorrhage can probably be considerably reduced by early recognition and management, which has only recently been described.[76,77]

Atherosclerotic Disease

Percutaneous transluminal angioplasty of brachiocephalic vessels, including the innominate, subclavian, vertebral, and external and internal carotid arteries, is now being performed in selected cases. This technique appears to be safe and effective in treating hemodynamically significant lesions. Follow-up has included angiographic and clinical evaluation for as long as four years and has shown gen-

*References 6, 7, 19, 21, 22, 67-70, 72-75.

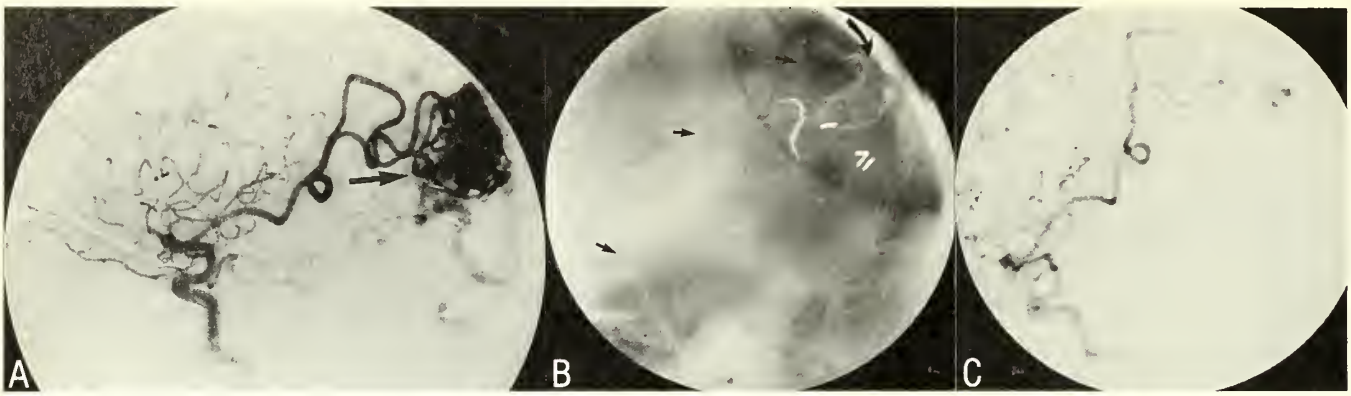

Figure 2.—A, Left internal carotid artery catheterization, lateral view, shows a left occipital lobe arteriovenous malformation **(arrow)** in a 48-year-old man with seizures. An attempt to remove the malformation 10 years ago was stopped because of uncontrolled bleeding. **B,** Left middle cerebral artery distal branch catheterization, lateral view, shows supply to the malformation **(curved arrow)**. The course of the catheter is shown **(straight arrows)**. Three other arterial pedicles similar to this one were catheterized, tested with sodium amobarbitol, and embolized with platinum coils and polyvinyl alcohol particles. **C,** Left internal carotid artery catheterization, lateral view, shows minimal residual filling of the malformation. The mass of mostly thrombosed vessels was surgically excised without difficulty.

erally stable clinical and angiographic results. Among 165 patients treated, there was a successful angiographic result in 162.[78-83] Lesions most commonly treated were in the common carotid or internal carotid artery, although there is beginning to be extensive experience with all the vascular areas. Of the 165 patients, 3 either had residual stenosis or the angioplasty catheter could not be advanced across the stenotic lesion.[78,79] Two patients had restenosis in follow-up.[80] Temporary ischemic complications occurred in five patients.[80,81] There was only one permanent stroke, in a patient with basilar artery atherosclerotic disease.[79]

Despite the promising results of this form of therapy, acceptance of this treatment is not widespread. There is a valid concern of distal embolization of debris from the plaques subjected to angioplasty, and this problem has been shown to occur.[84] The clinical results would suggest, however, that distal embolization is seldom serious. Recurrent stenosis from myointimal hyperplasia is another concern with this technique, as with the surgical technique.[85] The initial reports with long-term follow-up do not show this problem to be especially prevalent.

Carotid-Cavernous Arteriovenous Fistulas

Carotid-cavernous fistulas are of two types, direct or indirect. The direct fistulas are usually solitary connections between the cavernous segment of the internal carotid artery and the cavernous sinus. Most of these direct types are the result of head trauma or rupture of intracavernous carotid artery aneurysms. Indirect, or dural type, carotid-cavernous fistulas are usually composed of multiple connections between branches of the internal and external carotid arteries and the veins in the cavernous sinus. These indirect fistulas are usually spontaneous in origin, characterized by slow flow, and associated with a higher rate of spontaneous closure. Carotid-cavernous fistulas of either type may result in a loss of vision, bruit, exophthalmos, glaucoma, ophthalmoplegia, or intracranial hemorrhage. These signs and symptoms may require urgent treatment.[86]

The treatment of choice for direct carotid-cavernous fistulas is transarterial embolization with the preservation of flow through the internal carotid artery.[87] In a series of 206 patients with direct carotid-cavernous fistulas treated by transarterial balloon embolization, 88% had the fistula closed with a preservation of flow through the carotid artery.[88] Closure of the internal carotid artery was required in 12% of patients to close the fistula. The complication rate for strokes was 2.4%.

Transarterial embolization may also be done with platinum wires. This approach has been used successfully in cases where balloons were ineffective because of difficulty in navigating them into the fistula or because sharp spicules of bone break the balloon each time it is inflated. In a series of five patients, the fistula was closed in three, with the preservation of flow through the internal carotid artery.[89] One patient had a carotid occlusion when a coil was partly left in the internal carotid artery. The other patient's fistula could be closed only with a balloon in addition to the coils.

When transarterial embolization of direct carotid-cavernous fistulas is unsuccessful, alternative treatments are available. Transvenous embolization has been described as an effective approach to treating these lesions. In a series of 12 patients treated, 11 were completely cured and 1 had subtotal occlusion of the fistula with abatement of clinical symptoms.[90] A direct surgical exposure of the cavernous sinus can be performed for closing these fistulas by packing with wires or balloons, although this procedure is seldom necessary.[91]

The treatment of choice for indirect, or dural, carotid-cavernous fistulas is through a transvenous route.[92] The multiplicity of arterial feeders going into these fistulas makes the transarterial route less likely to succeed because if any arterial inflow remains, it will likely hypertrophy and the fistula will reform. Access to the cavernous sinus fistula is most commonly obtained through the inferior petrosal sinus. Among 13 patients treated by this approach, the fistula was closed completely in 12 and partly in 1.[92]

The superior ophthalmic vein is another route used in the transvenous approach. This vein may be reached by either the femoral percutaneous approach or by exposure of the angular vein in the face, which leads into the superior ophthalmic vein. This approach has been used in four patients with complete closure of the fistula in all four.[93] Other reports of the superior ophthalmic vein approach have also described it as being successful.[94,95]

Dural Arteriovenous Fistulas

Dural arteriovenous fistulas represent 10% to 15% of all arteriovenous malformations.[96] They occur most often in the

region of the transverse and sigmoid sinus, although they may occur in any region of the head where dura is found, including the superior sagittal sinus, inferior petrosal sinus, anterior cranial fossa, and around the deep cerebral venous system or vein of Galen.[97-101] In adults, these lesions are thought to be acquired from small vessels that form in a thrombosed sinus or vein.[102] Although most dural sinuses develop spontaneously, trauma and hypercoagulable states have been suggested as predisposing factors to the development of some fistulas.[102]

The presentation of these fistulas includes pulse-synchronous tinnitus or bruit, headache, loss of vision, an altered mental state, and neurologic deficits.[103] Dural fistulas may also cause intracranial hemorrhage. The pattern of venous drainage from these lesions accounts for most of the symptoms. High-flow fistulas that drain into a large sinus usually have a bruit. The drainage of arterialized veins into the cavernous sinus region or orbital veins may produce deficits of ocular movement, proptosis, or loss of vision. Drainage into veins in the brain may result in headache, neurologic deficits from venous hypertension, or hemorrhage from the rupture of thin-walled veins carrying blood under increased pressure.

The treatment of dural arteriovenous fistulas may be complex. Embolization through feeding arteries can ameliorate symptoms related to these fistulas, particularly lesions in certain anatomic locations such as the cavernous sinus. If transarterial embolization is incomplete, however—and it usually is—collateral supply will develop and symptoms may recur. Surgical therapy is difficult because of the tremendous blood flow into many of these lesions. There is a 15% rate of major morbidity and mortality for the surgical treatment of dural fistulas in the transverse and sigmoid sinuses, mostly related to massive blood loss or occlusion of the normal draining veins from the brain.[104] In certain locations, however, such as the anterior cranial fossa, the surgical treatment is preferred and usually successful with little morbidity.[98]

The most recent developments in treating dural arteriovenous fistulas include approaching these lesions through the draining vein and a combined approach of transarterial embolization, transvenous embolization, and surgical repair.[99,105,106] This combination of techniques has led to improved results in lesions that previously would have been difficult to treat. In a series of 16 patients treated by this combined approach, all patients were either cured or improved, and there was no serious permanent morbidity.[105] These combinations of treatments have also led to improved results in lesions that heretofore were considered almost untreatable, as in the deep cerebral venous system around the vein of Galen, although in infants with congestive heart failure, the morbidity and mortality remain high.[101]

Direct Endovascular Thrombolytic Therapy for Dural Sinus Thrombosis

Spontaneous thrombosis occasionally occurs in cerebral veins or dural sinus. This type of thrombosis is different from that occurring as a result of an infectious process. Dural sinus thrombosis may exhibit a wide spectrum of clinical findings, ranging from asymptomatic incidental findings to catastrophic fatal courses.[107-116] Patients with symptomatic dural sinus occlusion commonly have headaches, papilledema, seizures, and focal neurologic deficits. The natural history of a dural sinus thrombosis that produces occlusion is also variable. The reported mortality ranges from 10% to 50%.[107,112] The lower mortality may be related in part to the diagnosis of asymptomatic sinus thrombosis. Factors thought to be of prognostic importance, such as the rate of evolution of thrombosis, coma, patient's age, and involvement of cerebral veins,[107,113,114,116] have not been substantiated in a larger series.[112] Therefore, results seem to be unpredictable; some patients have a dramatic, spontaneous recovery, whereas others have a rapidly declining and often fatal clinical course. The natural history makes treatment regimens difficult to compare. For dural sinus thrombosis resulting from an infectious process, antibiotics are the mainstay of therapy. The therapy for spontaneous dural sinus thrombosis is more controversial. Surgical reconstruction of a thrombosed sinus has been described but has not gained widespread acceptance.[117] Heparin therapy is often used to prevent the additional spread of a thrombus, but this therapy is also controversial and does not affect the involved, occluded sinus directly. The use of high-dose peripheral urokinase therapy in conjunction with heparin was associated with clinical and angiographic improvement in two series of five patients each.[116,118] Others, however, have reported poor results from this therapy that apparently were related to intracranial hemorrhage.[107,116]

Recent reports have shown the successful use of local fibrinolytic agents for the treatment of dural sinus thrombosis in four of five patients.[108,110,119] Administering urokinase locally obviates the need for high doses that result in systemic fibrinolytic effects. In two patients, urokinase was infused locally by a catheter placed directly into the superior sagittal sinus. The catheter was placed by doing a burr-hole craniotomy in one patient and by a percutaneous puncture of the superior sagittal sinus through the anterior fontanelle in the other patient. More recently, catheterization of the superior sagittal sinus through the percutaneous jugular vein has been used with good results in two of three patients. There have been no serious complications from these approaches.

Scalp Arteriovenous Fistulas (Cirsoid Aneurysms)

Cirsoid aneurysms are abnormal arteriovenous communications that most often occur in the scalp or face. The fistulous connections are associated with a large draining vein or varix. The clinical manifestations relate primarily to the size of the fistula. The patients present with symptoms of loud bruits, hemorrhage, scalp necrosis, pain, throbbing headaches, and a cosmetic deformity. In the past, treatment consisted of surgical excision or ligation of feeding arteries.[120,121] Surgical therapy was necessarily extensive and often associated with excessive blood loss. If the operation was incomplete, the fistula would reform as collaterals developed.

Transarterial embolization of scalp arteriovenous fistulas has been done as definitive treatment or as an adjunct to treatment.[122] Arterial embolization often occludes vessels proximal to the fistula, however, and recurrence commonly develops due to the recruitment of collateral vessels. Embolizing a scalp arteriovenous fistula through the draining vein may be a more effective therapy when embolization is used alone.[123]

An approach that uses a variety of techniques has been most successful in treating these lesions.[124-126] These procedures all rely on depositing the embolic agent directly in the fistulous site, rather than in proximal arteries or draining

veins. These approaches may include selective arterial embolization using glue, coils, balloons, or silk suture. The fistulas may also be reached through a retrograde approach from the draining vein. This approach is particularly useful when the feeding arteries are so tortuous that the embolization catheters will not reach the fistula. Direct, percutaneous puncture of the fistula is also an effective therapy. Either absolute alcohol, glue, or wire coils can be placed in the fistula and produce thrombosis.

These combinations of techniques may lead to cure in 70% to 100% of patients treated.[124-126] Surgical intervention may be necessary to remove the thrombosed mass or small residual fistula in some cases, although blood loss should be minimal. Complications rarely occur and are usually related to necrosis of the overlying skin, particularly if alcohol has been misdirected into the subcutaneous tissues or there is a history of ischemia over the fistula. The surgical repair is typically a much easier procedure after the fistula has thrombosed.

Intra-arterial Fibrinolysis for Stroke

The use of fibrinolytic agents for the treatment of cerebral arterial occlusions was first clearly described by Fletcher and associates.[127] Enthusiasm was reduced by the high incidence of hemorrhagic complications that occurred in about 25% of the patients treated with the parenteral administration of urokinase. Local intra-arterial therapy has been tried and appears to be associated with a lower rate of hemorrhagic complications.[128] Using this selective delivery of urokinase, the posttreatment rate of hemorrhage has been reduced to 13%.[129] In one study, a series of patients with acute internal carotid or middle cerebral artery occlusion were classified into three categories based on the location of the occlusion.[130] The patients who had a patent circle of Willis and lenticulostriate arteries and those with distal middle cerebral artery occlusions did better than patients with occlusion of these areas. Only the patients in this last group had their treatment complicated by hemorrhage. Based on these findings, intra-arterial fibrinolysis is probably safe in the first two groups but may be unsafe in the group composed of patients with occlusion of the circle of Willis or lenticulostriate arteries if given four or five hours after the event. The efficacy of this therapy is not yet known, although several reports have noted success with the use of intra-arterial thrombolysis (Figure 3).[128-131]

Summary

Interventional neuroradiologic techniques are now available for various cerebrovascular disorders. The technical development of improved radiologic imaging, catheters, guide

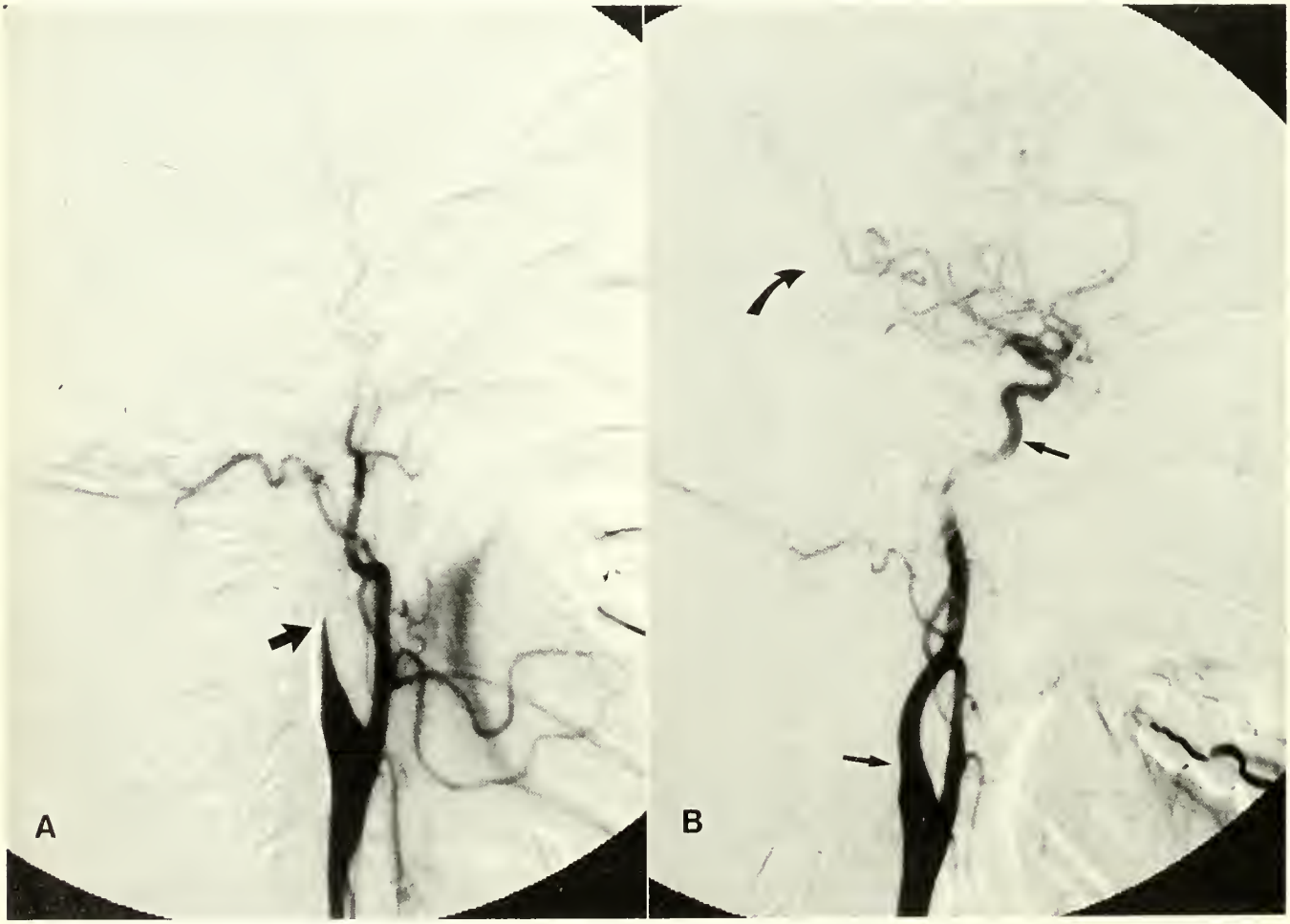

Figure 3.—A, Right common carotid artery catheterization, lateral view, in a 63-year-old man with atrial fibrillation who presented with abruptly occurring left hemiplegia. There is occlusion of the right internal carotid artery **(arrow)** by an embolus above the carotid bifurcation. The patient was treated with 900,000 units of urokinase administered by a Tracker-18 catheter (Target Therapeutics, San Jose, California) selectively into the internal carotid, middle cerebral, and anterior cerebral arteries. **B,** Right common carotid artery catheterization, lateral view, shows that the internal carotid artery is open **(straight arrows)**, as are most of the middle cerebral and anterior cerebral arteries. Some branches remain occluded **(curved arrow)**.

wires, and embolic agents has enabled this field to flourish. Many diseases for which there was previously no safe and effective therapy may now be treated. These techniques have been particularly useful in the management of unclippable cerebral aneurysms, vasospasm after aneurysmal subarachnoid hemorrhage, acute stroke, and large cerebral arteriovenous malformations. The techniques have also been useful as adjuncts or alternatives to surgical therapy for carotid-cavernous fistulas, dural and scalp arteriovenous fistulas, and arteriovenous malformations. As experience increases with these techniques and better embolic agents are developed, the complication rate of these procedures will decrease.

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Conferences and Reviews

Lumbar Spinal Stenosis

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Lumbar spinal stenosis, the result of congenital and degenerative constriction of the neural canal and foramina leading to lumbosacral nerve root or cauda equina compression, is a common cause of disability in middle-aged and elderly patients. Advanced neuroradiologic imaging techniques have improved our ability to localize the site of nerve root entrapment in patients presenting with neurogenic claudication or painful radiculopathy. Although conservative medical management may be successful initially, surgical decompression by wide laminectomy or an intralaminar approach should be done in patients with serious or progressive pain or neurologic dysfunction. Because the early diagnosis and treatment of lumbar spinal stenosis may prevent intractable pain and the permanent neurologic sequelae of chronic nerve root entrapment, all physicians should be aware of the different neurologic presentations and the treatment options for patients with spinal stenosis.

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Lumbar spinal stenosis is defined as narrowing of the neural canal and foramina to an extent that results in compression of the lumbosacral nerve roots or cauda equina. The embryologic and developmental factors that determine the anatomic configuration and dimensions of the spinal canal are poorly understood. As the articulating facets and supportive ligaments undergo degenerative hypertrophy and osteophytic ridges form, they encroach on neural structures passing through or exiting the spinal canal. Although the prevalence of spinal stenosis is difficult to determine because no population-based studies have been done, the disorder is relatively common and has been recognized more frequently since the introduction of advanced radiographic imaging techniques. A thorough understanding of the anatomic relationship of structures within the spinal canal is necessary to facilitate accurate diagnosis and appropriate surgical intervention.

Etiology and Pathogenesis

The amount of space available for nerve roots in the lumbar spinal canal and foramina is determined both by spinal developmental variations and by articular degenerative responses. The morphogenesis of the lumbar vertebrae begins after the seventh week of gestation, when a pair of chondrification centers forms in each vertebral arch (Figure 1).[1,2] Ossification and bony union of the centrum with its neural arch define the dimensions of the neural canal and foramina and are not completed until several years after birth.[3] If the paired dorsolateral ossification centers of one or more lumbar vertebrae stop growing prematurely, the lumbar spinal canal may become stenotic even in an otherwise normally developed person.[4]

The vertebrae of patients with congenital lumbar stenosis are characterized by short and thick pedicles. The transverse interpediculate diameter may also be smaller than the normal distance of 25 mm.[5] The vertically oriented laminae are short and thick, bringing the facets almost to the midline.[6] The facets are enlarged and bulbous and may nearly touch the spinous processes. Although primary lumbar stenosis is the sole cause of entrapment radiculopathy in only 2% of patients with sciatica at presentation, it is a contributing factor associated with superimposed disc herniation or spondylosis in 30% of these patients.[7]

Stenotic lesions can occur in any of three anatomic sites: the central canal, bordered by the vertebral bodies, discs, and articular processes; the subarticular canal or lateral recess, which extends from the thecal sac to the pedicle; and the intervertebral foramen or nerve root canal lying below the pedicle.[8,9] Stenosis in the central canal usually results from concomitant ligamentous hypertrophy and disc protrusion, especially in patients with a congenitally small spinal canal. Stenosis in the lateral recess is caused by degenerative ligamentous and superior facet hypertrophy. In the foramen, stenosis may result from osteophyte formation under the pars interarticularis where the ligamentum flavum is attached, or from bursal tissue hypertrophy at a spondylolytic defect. The clinical presentation of stenosis is similar at each of these anatomic sites, and the site can be determined only with radiographic imaging.[9-12]

Several important variations of lumbar stenosis are unilateral stenosis caused by a short pedicle, asymmetric stenosis caused by unequal posterior hypertrophy, discontinuous or skipped levels of stenosis, a normal canal in the midline with constricted lateral recesses, a narrow canal in the midline with normal lateral recesses, and sacral stenosis.[13-15] These variations are difficult to diagnose with plain films or standard myelography, but computed tomography (CT) with intrathecal contrast and magnetic resonance imaging (MRI) allow them to be more easily recognized.[16]

Lumbar spinal stenosis can be either congenital or acquired. Congenital or developmental stenosis was described originally in children by Sarpyener and later in adults by Verbiest and is most frequently caused by an idiopathic reduction in the normal spinal canal dimensions or by achondroplastic dwarfism.[17,18] Verbiest performed decompressive laminectomy in middle-aged men who had radicular symptoms in the lower extremities that were aggravated by walking or standing. In all of these patients, the anteroposterior

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
MRI = magnetic resonance imaging

diameter of the lumbar spinal canal was 12 mm or less, much smaller than the 15- to 23-mm diameter in normal cadaver skeletons.[19] Reports of familial developmental lumbar stenosis suggest that the dimensions of the spinal canal, at least in some patients, are regulated by genetic factors.[20,21]

Developmental stenosis of the entire spinal canal is a well-known feature of achondroplastic dwarfism.[22] The vertebrae of patients with this disorder have short pedicles and decreased interpediculate distances, resulting in both anteroposterior and lateral stenosis of the canal. As adults, these patients often have syndromes involving progressive compression of the spinal cord or cauda equina.[4] Minor trauma and disc extrusion in the thoracic or lumbar spine may cause the sudden onset of flaccid or spastic paraplegia. The vertebral deformity has been explained by premature cessation of growth of the paired vertebral body and dorsolateral neural arch ossification centers.[23]

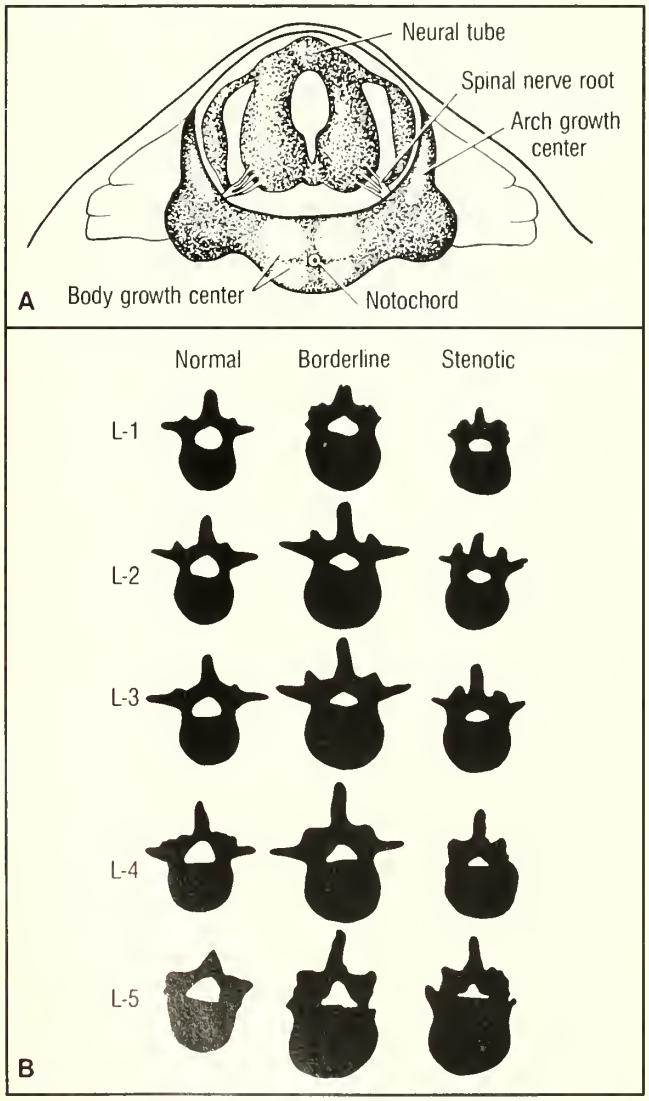

Figure 1.—**A,** The diagram of lumbar vertebral embryogenesis illustrates paired vertebral body chondrification sites, which unite at 9 weeks' gestation to form a single growth center. Premature cessation of vertical growth in the paired pedicle growth centers could explain developmental stenosis caused by a failure of the neural arch to achieve adequate dimensions (from Weinstein[1]). **B,** Photo tracings of three sets of cadaver lumbar vertebrae show developmental variations in the size and shape of the neural canal, with **A** being normal, **B** borderline, and **C** stenotic. In the stenotic examples, the typical trefoil shape with severe narrowing of the lateral recesses is seen at L-5 (adapted from Epstein et al[2]).

Acquired lumbar stenosis is caused primarily by degenerative disease of the spine. Spontaneous or posttraumatic tears, degeneration, fibrosis, and collapse of the disc lead to the failure of mechanical function and then to subperiosteal osteogenesis at sites where the herniating annulus is attached to the junction of cartilaginous plates with the epiphyseal ring of the vertebral body lip.[24,25] As patients grow older, biomechanical failure of the lumbar discs increases the stress on facet joints and ligamentous attachments, resulting in hypertrophy of the facets and ligaments.[26] Bone also thickens at the pedicles, laminae, and facets as a result of chronic stress or repeated minor trauma.[27-31] A loss of disc height further narrows the neural foramina as the superior facets migrate rostrally. Collapse of the disc reduces the interlaminar space, narrowing the spinal canal as the dorsal edge of the upper lamina overrides the rostral edge of the lower lamina.[27] Posterior protrusion of the annulus and disc contributes to stenosis and nerve root entrapment in the midline, lateral recesses, and foramina.[32]

Degenerative spondylosis is usually associated with hyperplasia, fibrosis, and cartilaginous metaplasia of the annulus, posterior longitudinal ligament, and ligamentum flavum. This disease may increase the thickness of the ligamentum flavum from its normal of 2 to 5 mm[33] to as much as 5 to 10 mm in patients with spondylosis.[1] In our experience, hypertrophied ligamentum flavum causes the most notable compression of the neural elements, and it may be the major cause of lumbar stenosis in some patients.[13,25,34,35] Histologic examination of surgical specimens of ligamentum flavum reveals fragmentation, degeneration, and disappearance of elastic fibers that do not regenerate after injury.[36] These specimens also show increased vascularity, resulting in excessive collagen deposition and fibrosis[1]; evidence of old hemorrhage and residual granulation tissue are occasionally found.[37]

Both spondylolysis (a defect in the pars interarticularis) and spondylolisthesis (the relative anterior or posterior displacement of one vertebral body on an adjacent vertebra) can contribute to spinal stenosis. In degenerative spondylolisthesis, a frequent complication of advanced lumbar spondylosis,[13] complete myelographic block can occur as a result of associated posterior ligamentous and facet hypertrophy in patients with only 3 to 4 mm of subluxation. Because the neural arch is intact, the term "pseudospondylolisthesis" has been used to describe this condition.[27] Disc protrusion and anterior and superior migration of the superior facet may completely obliterate the foramina.

Although acquired spinal stenosis is usually caused by spondylosis and spondylolisthesis, a number of rarer causes exist. Vertebral deformities, osteophyte formation, and soft tissue calcification are frequent sequelae of disc-space infection, osteomyelitis, and Pott's disease (tuberculosis of the spine).[38] Moreover, calcification or ossification of the posterior longitudinal ligament or ligamentum flavum and the development of intraspinal synovial cysts may contribute to spinal stenosis.

Other causes of acquired stenosis are surgical procedures

(laminectomy or spinal fusion),[39] trauma,[40] and bony overgrowth. This overgrowth may be associated with Paget's disease (osteitis deformans),[41] ankylosing spondylitis,[42,43] diffuse idiopathic skeletal hyperostosis,[44] or rheumatoid arthritis.[45] Finally, various metabolic and endocrine abnormalities, such as acromegaly,[46] pseudogout, hypoparathyroidism, or renal osteodystrophy,[47] have been associated with lumbar stenosis (Table 1). Radiculopathy may also be caused by epidural lipomatosis, which is seen predominantly in patients with endogenous obesity who are taking steroids or who have Cushing's syndrome.[48]

Clinical Features

Patients with lumbar spinal stenosis may present with a variety of signs and symptoms. One such symptom is neurogenic claudication, characterized by poorly localized leg pain, sometimes associated with numbness and weakness. This pain is exacerbated by walking or standing and is relieved by postures that reduce the degree of lumbar lordosis.[38,49,50] Patients also usually report a progressive reduction in the distance they can walk before symptoms are noticed. Pain is usually felt before numbness and weakness and has a radicular pattern, unlike the "cramping calf" pain described by patients with vascular claudication. The symptoms typically resolve after two to five minutes of rest in a leaning or sitting position. The pain may be bilateral and poorly localized in stenosis of the central canal, or it may be well localized to one or more nerve roots when lateral recess stenosis predominates.[38,50-52] Claudication is usually bilateral, but asymmetric canal stenosis sometimes causes unilateral symptoms. All of these symptoms may be preceded by chronic low back pain, and they often follow a gradually progressive and prolonged course. The disorder is far more common in men than in women and requires surgical treatment more often in men.[5,50,53]

TABLE 1.—*Major Causes of Spinal Stenosis*

Congenital-developmental stenosis
Idiopathic
Achondroplasia or hypochondroplasia
Hypophosphatemic vitamin D-resistant rickets
Morquio's mucopolysaccharidosis
Spinal dysraphism
Acquired stenosis
Degenerative
Spondylosis
Spondylolisthesis
Scoliosis
Ossification of the posterior longitudinal ligament
Ossification of the ligamentum flavum
Intraspinal synovial cysts
Postoperative
Laminectomy
Fusion
Posttraumatic
Metabolic or endocrine
Epidural lipomatosis—Cushing's disease
Osteoporosis
Acromegaly
Pseudogout—calcium pyrophosphate dihydrate deposition disease
Renal osteodystrophy
Hypoparathyroidism
Other
Paget's disease of bone
Rheumatoid arthritis
Ankylosing spondylitis
Diffuse idiopathic skeletal hyperostosis

The pathogenesis of nerve root dysfunction in patients with neurogenic claudication, characterized by poorly localized leg pain exacerbated with walking and relieved by rest or back flexion, is unclear. Pain and weakness may result from intermittent ischemia caused by compression of the radicular microcirculation during periods of increased axonal activity.[54-58] During tourniquet constriction, nerve fibers first become hyperexcitable and then fire volleys of spontaneous afferent impulses.[56] Later, reversible blockade of conduction by sensory or motor fibers may occur, possibly accounting for the sequence of pain and paresthesias followed by weakness seen in patients with neurogenic claudication.

Positional radiculopathy is a more common initial symptom of lumbar stenosis than is neurogenic claudication and is manifest as radiating leg pain, paresthesias, numbness, or weakness occurring when the patient stands erect or bends backward. Lumbar spine extension induces radiculopathy by relaxing and buckling the ligamentum flavum; it also increases disc protrusion.[59] Extension also moves the laminae closer together and projects the superior facets farther upward, further narrowing the spinal canal and foramina by as much as 60% compared with their diameter during lumbar flexion.

The cauda equina syndrome, characterized by intermittent or progressive symptoms of urinary or fecal incontinence, impotence, and sensory loss in a saddle distribution, is an infrequent presentation of lumbar spinal stenosis. In patients with stenosis, symptoms may be related to standing or walking, whereas in patients with acute disc herniation, symptoms occur abruptly. The symptoms may not be recognized by the patients, making rectal examination an invaluable part of the neurologic examination.

Demonstrable sensory or motor deficits are often absent in patients with lumbar stenosis. Because spinal stenosis has a predilection for the midlumbar spine,[38,60] quadriceps weakness or atrophy and a depressed or absent knee jerk may be the only physical findings. Some patients describe the onset of major weakness such as a footdrop only after prolonged ambulation. The results of the straight-leg-raising test are usually normal, perhaps because this sciatic stretch maneuver also flexes the lumbar spine, thus relieving compression of the nerve roots caused by stenosis.[38,59]

Diagnosis

When a patient's history and the results of the physical examination suggest lumbar stenosis, the diagnosis may be confirmed by other tests. Because of the expense and invasiveness of radiographic imaging techniques, however, further diagnostic workup of patients with suspected lumbar spinal stenosis should be reserved for those with progressive neurologic deterioration, intractable pain, or cauda equina syndrome, or for those in whom surgical intervention is anticipated.

Myelography followed by thin-section CT has been the radiographic imaging modality most often used to demonstrate neural encroachment.[61-64] Defects apparent on myelography range from an "hourglass" configuration to complete obstruction of the subarachnoid space.[65] Computed

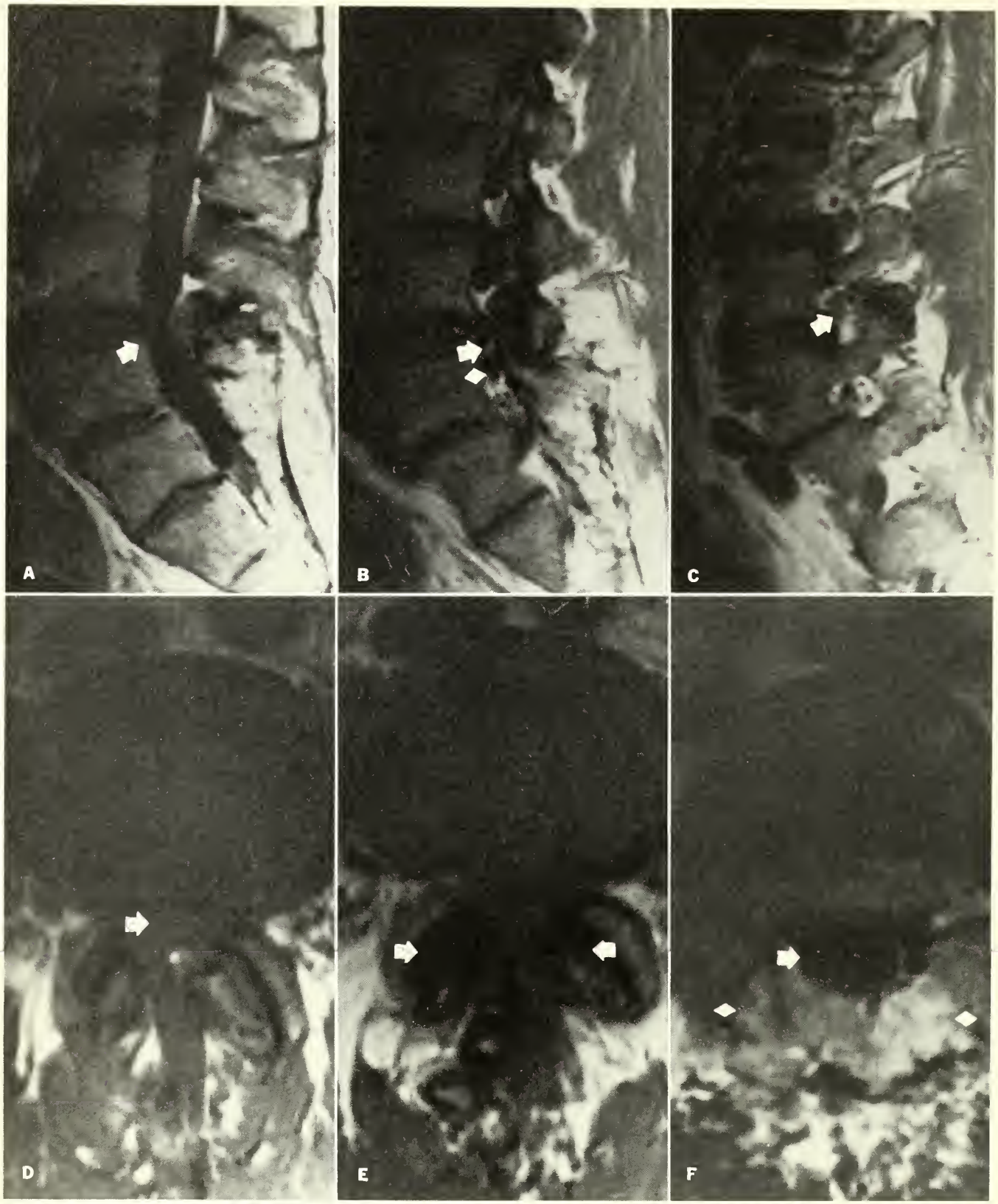

Figure 2.—Magnetic resonance images are shown of a 72-year-old man with intractable bilateral leg pain in the L-5 distribution, initiated and aggravated by standing erect and walking. He had undergone an L5-S1 discectomy and fusion 5 years previously. The results of the neurologic examination and the straight-leg-raising test were normal. The midline image in the sagittal plane, **A,** shows dorsolateral encroachment with stenosis of the neural canal (**arrow**) that is most severe at L3-4. The left lateral sagittal image, **B,** shows L3-4 lateral recess stenosis (**arrow**) caused by disc bulge anteriorly and by hypertrophy of the superior facet posteriorly. The nerve root (**diamond**) is compressed. **C,** Only minimal foraminal narrowing is seen (**arrow**) in the far lateral image. **D,** Axial images confirm almost complete obliteration of the subarachnoid space and constriction of the thecal sac (**arrow**) at L3-4 by dorsal facet, ligamentous hypertrophy, and a ventral discogenic osteophyte. **E,** Moderately severe stenosis seen at L4-5 is primarily a result of hypertrophy of the facets (**arrows**). **F,** The rounded triangular thecal sac configuration (**arrow**) of a relatively normal canal is seen beneath the fusion mass (**diamonds**) at L-5. This patient returned to unrestricted work and recreational activities including playing golf and tennis within 2 months after an L-4 laminectomy with bilateral foraminotomies at L3-4 and L4-5.

tomography allows the configuration and dimensions of the canal to be determined and the contribution of disc displacement, facet and soft tissue hypertrophy, and spondylolysis or occult fractures to be recognized.[63,66,67] Sagittal reconstructions can provide a clear picture of the neural foramina and the relationships of the exiting nerve roots to the pedicles and facets. Computed tomography using a water-soluble intrathecal contrast agent is more sensitive than myelography, which often fails to distinguish posterior from anterior sources of nerve root compression and does not demonstrate the configuration of the lateral recesses and foramina.[16,68-70] Contrast-enhanced CT is especially helpful in patients with persistent postoperative symptoms.[67,71,72]

The features of spinal stenosis apparent on CT are broad-based disc bulging with or without a vacuum disc phenomenon, a congenitally small neural canal, hypertrophic facet disease or facet cyst formation, and ligament hypertrophy.[60] On images taken through the level of the disc space, decreased sublaminar epidural fat is a good indication of spinal stenosis; on images taken through the level of the pedicle, however, this may be a normal finding.[73-75] Some fat may be seen in the midline beneath the spinous process even in patients with severe sublaminar and subarticular stenosis.

Magnetic resonance imaging, when available, is an alternative to CT in the radiographic diagnosis of spinal stenosis. Its advantages include the lack of radiation, the avoidance of invasive intrathecal contrast administration, and the capability of direct multiplanar image construction. In addition to its greater sensitivity in detecting disc disease, MRI also allows visualization of the entire lumbosacral and lower thoracic spine, as well as the conus medullaris and cauda equina (Figure 2).[76] Although MRI provides better soft tissue detail than CT,[77,78] particularly in the lateral recess, it does not provide the detail of bony structures available with CT.[75] Nevertheless, we agree that high-quality MRI should now be considered the most effective and least invasive modality for spinal imaging.[76-78]

The results of electrodiagnostic studies are more often abnormal than are those of the neurologic examination.[51,79] In nearly 80% of patients with proven stenosis, electromyography demonstrates radiculopathy.[61] Abnormalities are often bilateral and involve several root segments. Electromyography is particularly useful in stenosis of the lateral recesses, which may be overlooked if only routine or poor-quality spinal radiographic studies are available. Normal neurophysiologic studies, however, do not rule out spinal stenosis because radiculopathy may be intermittent and evident only after standing and walking.

Plain radiographs may show degenerative changes that contribute to canal stenosis, such as spondylosis and spondylolysis, or underlying bone diseases, such as Paget's disease or dwarfism.[38,80-82] The canal diameter can be measured from anteroposterior and lateral lumbar spinal radiographs, but these measurements are less important than the configuration of the spinal canal as visualized with axial scanning at various levels.[61,83] Although plain radiography is an inexpensive initial diagnostic study, the diagnosis of lumbar spinal stenosis cannot be made on the basis of plain films alone.

Treatment

Conservative, nonoperative therapy includes nonsteroidal anti-inflammatory medications and exercise programs to strengthen abdominal musculature and reduce lumbar lordosis.[38,84] Bed rest, opiate analgesics, muscle relaxants, and lumbosacral bracing may help during periods of increased pain.[47] In our experience, some patients may benefit from a brief course of systemic steroid therapy or from a series of epidural steroid injections, administered under fluoroscopic control, below the level of stenosis. No large controlled studies have been published, however, that address the efficacy of steroid therapy in the treatment of lumbar stenosis. The use of an exercise bicycle, which allows aerobic activity and strengthens the back and leg musculature while the lumbar spine is flexed forward, may be better tolerated than walking. These treatments have been shown to diminish symptoms in some patients with lateral recess stenosis[70] and should be tried in all patients who do not have significant neurologic deficits such as weakness or sphincter disturbances. Medical management may be the only alternative in elderly patients with substantial systemic illness in whom surgical treatment is contraindicated.[85] Although these nonoperative measures may provide temporary relief, they usually do not prevent the recurrence of painful radiculopathy when normal activity is resumed.

Surgical intervention should be considered when medical management fails to relieve intolerable pain during activities of daily living. It should also be considered in patients with initial signs and symptoms of cauda equina dysfunction or progressive neurologic deterioration. Many surgical approaches have been described.[6,13,84,86-92] The goal of each of these approaches is to decompress the thecal sac and exiting nerve roots while minimizing the possibility of subsequent spinal instability.

The degree of surgical decompression must be individually tailored to the patient on the basis of clinical, radiologic, and surgical observations. Wide laminectomy with bilateral foraminotomies is the standard decompressive operation (Figure 3, left).[38,91] When this technique is used, postoperative spinal instability occurs in about 2% of patients older than 35 years,[93] although rates as high as 15% have been reported.[94] Fusion of the spine is therefore generally not necessary except in patients with degenerative spondylolisthesis in whom the likelihood of instability after decompression is high.[84,86,95] Internal fixation with instrumentation and fusion may also be necessary in patients with scoliosis.[96] Arthrodesis may be done at a later date if necessary to relieve intractable back pain or to correct postoperative instability.

Patients with focal midline or lateral recess stenosis may be treated with a limited interlaminar exposure and bilateral laminotomies to remove hypertrophic bone, ligamentous tissue, and osteophytes (Figure 3, right).[91] Decompression of the lateral recesses requires resection of the medial third of both inferior and superior facets and additional undercutting of hypertrophic facet bone and ligament or joint capsule. Complete facetectomy is rarely required, but it may be done if necessary for complete decompression. In elderly patients with spondylosis, complete facetectomy is usually well tolerated if it is unilateral. Discectomy and the removal of ventral marginal osteophytes are rarely desirable in patients with lumbar spondylosis. Unless discs are extruded, they should not be removed because discectomy may increase the possibility of spinal instability after wide decompressive laminectomy and medial facetectomy.

Among patients treated surgically, 80% to 85% obtain good or excellent results, defined as the relief of symptoms and a return to the premorbid level of activity.[5,6,38,51,97-100]

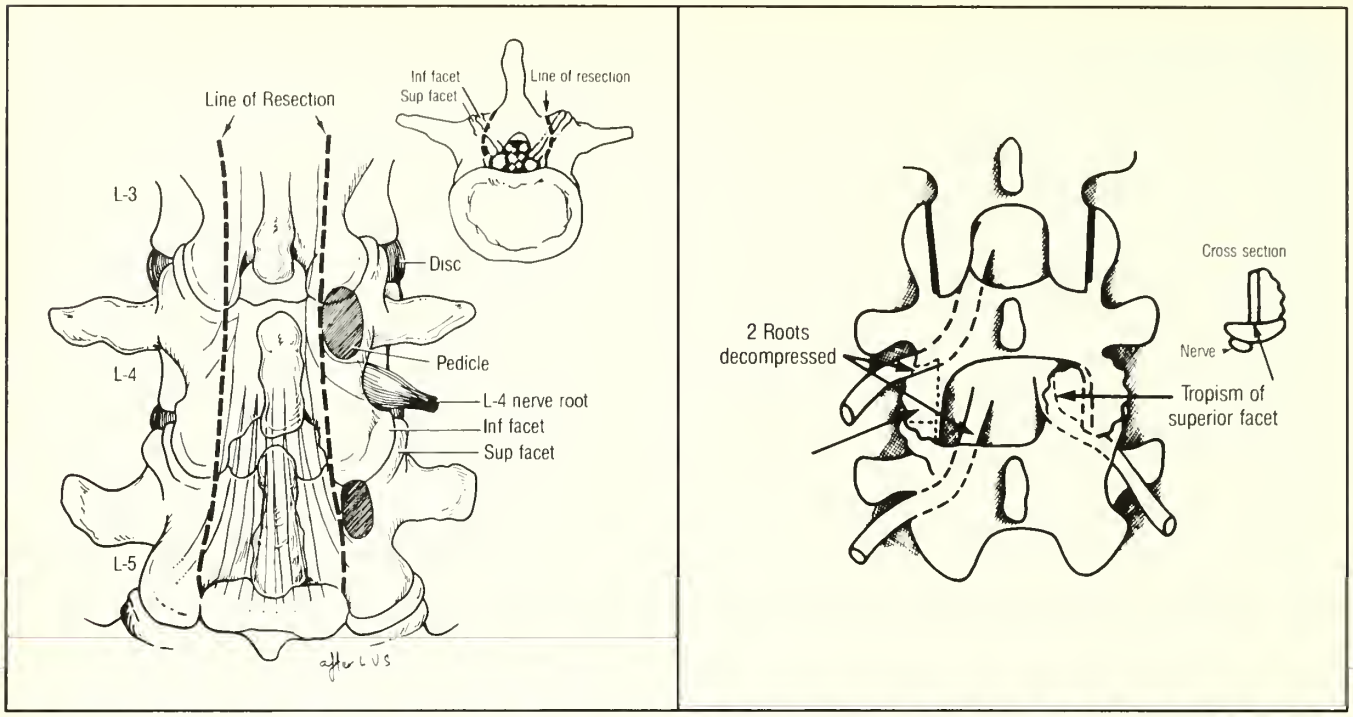

Figure 3.—Left, The diagram of decompressive laminectomy for lumbar spinal stenosis illustrates the extent of lamina and medial facet resection (**broken line**) required for adequate decompression of the neural canal and its lateral recesses. The axial view (**inset**) shows that the line of resection is placed parallel to the medial surface of the pedicle while sparing the lateral half of the facet. Hypertrophic laminae and facets are debrided and thinned with the power drill before completing removal with fine curettes and rongeurs. Inf = inferior, Sup = superior **Right,** The diagram shows the interlaminar approach for decompression of focal lumbar stenosis with bilateral laminotomies rather than a complete laminectomy. Using a microsurgical technique, the entire ligamentum flavum is exposed and removed along with the overlying facet (**arrows**) and laminar bone. Both the lateral recesses and foramina can be satisfactorily decompressed, leaving the lamina, spinous processes, and midline ligaments intact (from Lin[9]).

Many patients, however, are unable to return to work that requires strenuous lifting or prolonged walking or sitting. Because of the likelihood that irreversible nerve root damage has already occurred, full recovery should not be anticipated in patients with muscle atrophy and sphincter dysfunction. Mechanical low back pain is the symptom least often relieved after surgical decompression because this procedure alleviates nerve root entrapment but does not alter the underlying degenerative osteoarthritis that causes it.[39] The role of surgical fusion for internal fixation, with or without instrumentation and as either a primary or second-stage procedure, remains controversial.

Summary

Lumbar spinal stenosis, a common cause of painful and disabling radiculopathy initiated or aggravated by standing and walking, may not be diagnosed until irreversible neurologic damage has occurred. In elderly patients with spondylosis and symptoms of stenosis, MRI or CT with intrathecal contrast should be used to localize the site of nerve root entrapment. Although nonoperative treatment may be successful initially, surgical decompression should be done in patients with serious or progressive pain or neurologic dysfunction. Wide laminectomy or interlaminar decompression alleviates symptoms and improves physical capacity in most patients without interfering with spinal stability. Early diagnosis and treatment of spinal stenosis may prevent intractable pain and the permanent neurologic sequelae of chronic nerve root entrapment.

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Epitomes

Important Advances in Clinical Medicine

Pediatrics

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in pediatrics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in pediatrics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pediatrics of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Recent Advances in Pediatric Liver Transplantation

THE FIRST SUCCESSFUL LIVER transplantation was done on a child in 1967. Before 1980, liver transplants in children were rare because of the low, 20%, five-year survival rate. In addition, the high-dose corticosteroid immunosuppression caused severe debilitating side effects, including life-threatening infections, growth retardation, cataracts, and osteopenia. With the introduction of cyclosporine to the immunosuppressive regimens, the five-year survival rate has improved to 60% to 70%, and the dosage of corticosteroids has been lowered so that side effects are substantially reduced. In addition, a new preservation solution (University of Wisconsin solution) and rapid en bloc harvesting techniques have helped reduce the 20% incidence of immediate liver graft failures to less than 2%. With these improvements, liver transplantation has become accepted for the treatment of end-stage liver disease. Morbidity and mortality in infants, however, remained high. Of infants with end-stage liver disease, 25% to 50% died before transplantation because appropriate donors could not be found for infants weighing less than 10 kg. Infants who received transplants had only a 40% one-year survival rate.

Over the past five years, dramatic changes in the surgical management of infants have increased the survival rate. Perhaps the most important is the ability to use a portion or a lobe from an adult liver (reduced-size liver transplant). Thus, an adult liver, often weighing ten times more than the infant's liver, can be used. In addition, reduced-size liver transplants allow an adult donor's large hepatic artery to be used, thereby reducing the risk of hepatic artery thrombosis and graft failure from 20% to 5%.

The use of living-related donors has further helped in obtaining reduced-sized livers for small children when cadaver donors are not available. The success of using a living-related transplant is comparable to a cadaver transplant but provides the advantage that transplantation can be done electively before severe, irreversible complications of the liver disease have developed.

Newer immunosuppressive agents increase the hope for fewer side effects in the future. One such agent, FK 506, is an effective immunosuppressive drug without the known side effects of cyclosporine, such as hirsutism, gingival hyperplasia, coarsening of facial features, and hypertension. Also, FK 506 is better absorbed than cyclosporine postoperatively and during times of gastrointestinal infection. It has side effects that include insomnia and renal toxicity, however.

With improved medical and surgical management, 95% of infants and children with liver failure will now survive long enough to receive a transplant. More than 80% of children with transplants are expected to survive more than five years with minimal morbidity. The current average cost of $140,000 per liver transplant—ranging from $60,000 to $500,000—will decrease. The recent use of xenografts (nonhuman donors, such as pigs and baboons) remains controversial. The potential benefits of using xenografts include an increased availability of donors and reduced costs for organ procurement.

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Pain Management in Pediatrics

UNTIL RECENTLY, anesthesia and analgesia were not administered to newborns and infants during surgical and invasive procedures because of the concern that the risk of cardiovascular complications outweighed the benefits of pain relief and a smoother operative course. Current physiologic and behavioral research shows that general and local anesthesia are beneficial and carry minimal risks when combined with appropriate monitoring and close clinical observation. Recent studies have shown reduced morbidity and mortality in newborns undergoing major operations who received a general anesthetic and judicious use of opioids postoperatively, presumably by blunting catabolic stress responses.

Improved pain control in children can be achieved with patient-controlled analgesia pumps, continuous opioid infusions, continuous epidural infusions, and topical analgesic agents. Patient-controlled analgesia pumps now permit children as young as 7 years and, in selected cases, as young as 5 years, to adjust their pain medications to their individual needs through this computer-programmed device.

A continuous infusion of opioids, primarily morphine, provides excellent pain relief to younger children and those otherwise unable to use a patient-controlled analgesia pump. These infusions maintain a steady level of pain relief and eliminate oversedation immediately after an intravenous dose and inadequate pain relief before the next injection.

Epidural analgesia has proved to be a safe adjunctive measure to decrease general anesthetic requirements and provide postoperative pain relief for children undergoing a wide range of major surgical procedures. Catheters can be placed in the epidural space by the caudal (sacral), lumbar, or thoracic routes after the initiation of general anesthesia, to provide excellent postoperative pain relief with less of the sedating and respiratory depressant effects of systemic narcotics. Long-acting local anesthetics such as bupivacaine hydrochloride with or without concomitant opioids can be used in concentrations low enough to minimize motor dysfunction and yet provide effective pain relief.

Topical anesthetics such as EMLA (a eutectic mixture of prilocaine hydrochloride and lidocaine) are effective through intact skin and can greatly diminish the pain associated with painful procedures commonly done on children, such as venipunctures, intravenous cannulation, and spinal taps. Although used extensively in Europe, EMLA has just recently received approval by the Food and Drug Administration and is now available in the United States.

Chronic or recurrent pain in children (such as headaches and abdominal pain) is often managed by a multidisciplinary approach combining physical therapy, transcutaneous electrical nerve stimulation, relaxation, biofeedback, life-style alterations, stress management, supportive counseling, and the judicious use of medications. Neuropathic pain syndromes, including phantom limb pain and reflex sympathetic dystrophy, can be disabling and are often refractory to standard orthopedic treatments. Reflex sympathetic dystrophy, most common in female adolescent athletes, involves a pattern of intense pain to touch and sympathetically mediated hypoperfusion in an area of earlier injury. Physical and psychological therapy may be helpful along with low doses of tricyclic antidepressants that have shown particular efficacy in treating certain types of neuropathic pain in adults. When these measures prove ineffective, sympathetic nerve blocks can be done to provide pain relief, often with long-lasting results.

With the many new, safe, and effective methods to provide pain relief to children, it has become easier in the past few years to make children more comfortable during and after necessary medical procedures. Neuropathic pain syndromes continue to provide an important challenge to health care professionals and will most likely be a major topic of pain research for years to come.

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Advances in the Management of Childhood Asthma

INFLAMMATION IS NOW THOUGHT to play a central role in the pathophysiology of asthma. This diffuse eosinophilic inflammatory process leads to a state of increased airway reactivity or hyperresponsiveness in people with asthma. This means that the airways will respond with constriction to lesser amounts of stimuli, such as exercise or antigens, and that an asthma attack can occur more rapidly.

Because of the role of inflammation in asthma, recommendations for the treatment of chronic asthma have changed. Patients who have more than occasional symptoms of asthma should be treated continuously with anti-inflammatory agents by inhalation. Two classes of drugs that are anti-inflammatory are cromolyn and steroids. When these are taken over time, airway responsiveness improves.

Because of its safety, cromolyn sodium is recommended as the first medication to be used in children with asthma. It should be given three to four times a day; when the asthma is under control, the frequency can often be reduced. Some patients require an increase in the dosage when the pollen season begins. Cromolyn can also be used on an intermittent basis before exercise or before antigen exposure. It is important to know that cromolyn is available in a nebulizer solution, 20 mg per vial, in 20-mg capsules, and in a metered-dose inhaler, 1 mg per puff. Thus, if a patient is not responding to two puffs of the metered-dose inhaler four times a day, the number of puffs could be increased or the patient switched to the nebulizer solution.

Inhaled corticosteroids are effective anti-inflammatory drugs and should be added if the patient's asthma is not controlled with a regimen of cromolyn alone. In some patients it may be necessary only to add inhaled steroids on a seasonal basis when symptoms increase. Inhaled corticosteroids are thought to be safe when the dose is 400 μg or less a day. As the dose is increased, systemic effects, such as diminished growth rate, may occur. Different steroid preparations have different concentrations: beclomethasone dipropionate, 50 μg per puff; triamcinolone acetonide, 100 μg per puff; and flunisolide, 250 μg per puff. Inhaled corticosteroids should always be used with a spacer device in young children to prevent deposition of the drug in the mouth and vocal cords and to decrease local side effects, such as thrush.

Because the intermittent use of β-agonist bronchodilators results in a greater improvement in asthma than the continuous use, β-agonists should be used only on an "as-needed" basis for the treatment of acute asthma attacks and before physical activity in patients with exercise-induced asthma. Side effects include muscle tremor, a mild increase in heart rate, and a possible lowering of potassium levels. Theophylline remains an excellent bronchodilator but does not appear to have anti-inflammatory effects. It may be needed in patients who require continuous bronchodilation or who have nocturnal asthma. Serum concentrations of theophylline should be monitored and maintained at between 5 and 15 μg

per ml. Side effects from theophylline are dose dependent and include headache, nausea, nervousness, tachycardia, and, at toxic serum concentrations, seizures.

Inhaled medications can be administered to children in several ways. In children younger than 5 years, a compressor with nebulizer and mask is effective. Children 5 years and older often have some difficulty coordinating a metered-dose inhaler, so a spacer device—AeroChamber (Forest Pharmaceuticals, Inc) or InspirEase (Schering Corporation)—is helpful.

Peak-flow monitoring is essential for following the course of moderate to severe chronic childhood asthma. This simple maneuver can be used by physicians in their offices or in an emergency department to test the degree of airway constriction. Patients can record peak flows at home with inexpensive portable peak-flow meters and adjust medications before an asthma attack occurs. Peak-flow monitoring is most useful when related to a zone system based on the colors of traffic lights. Green zone—80% to 100% of personal best—means the asthma is stable and no change in medication is needed. Yellow zone—50% to 80% of personal best—signals caution and that an increase in medication, cromolyn or steroids, is needed. Red zone—less than 50% of personal best—signals danger and that immediate action is needed. A written action plan is helpful in instructing the patient and family on how to increase the medications.

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What's New in Chickenpox (Varicella-Zoster) Infection?

THREE DEVELOPMENTS promise to improve the clinical management of patients with varicella-zoster virus: vaccine release, oral acyclovir use in healthy children with chickenpox, and a new latex agglutination test.

Vaccine

Live attenuated varicella vaccine is expected to be licensed by the United States Food and Drug Administration in the spring of 1993 for use in all children and adults who have never had chickenpox. The vaccine was developed in Japan in the 1970s, and its use has been highly controversial in the United States. The arguments against the vaccine are that varicella is not severe enough a disease to warrant prevention by vaccine, that immunization with a vaccine that can cause latent infection (zoster) might increase the incidence of zoster, and that immunity after vaccination may not persist for a substantial period of time. Although the responses to these arguments remain incomplete, there are increasing data that varicella is not necessarily benign, that zoster is less common after vaccination than after the natural disease, and that children who have been immunized have immunity that persists for as long as ten years in long-term studies. In addition, women who contract chickenpox during the first or second trimester of pregnancy have a 2% chance of having a baby with the congenital varicella syndrome. A final argument is that many new immigrants are susceptible to varicella and may be candidates for immunization.

A mild case of chickenpox develops in about 15% of vaccinated children months to years after exposure to the virus. Antibodies to the virus develop in more than 90% of adults after two doses of vaccine, with 70% completely protected. Antibodies persist after vaccination for as long as ten years in 95% of healthy children and in 75% of children with leukemia and healthy adults. Important side effects from the vaccine are unusual, only 5% to 10% of vaccinees having a mild chickenpox rash that lasts a few days.

When the vaccine is first released, it will be available as a monovalent product, but within a few years it will most likely be combined with the measles-mumps-rubella vaccine and thus given twice during childhood. There is apparently no danger to immunosuppressed classmates as there has been no demonstrated spread of varicella-zoster virus from a healthy vaccinee to a contact. Spread has occurred in vaccinees who have leukemia, but even that is at a lower than normal rate (10% versus 80% to 90%) after household exposure and only if the vaccinee had a vaccine-associated rash.

Acyclovir

A large double-blind placebo-controlled study has shown that healthy children and adolescents who are given acyclovir within the first 24 hours of the chickenpox rash had a one-day-shorter course of varicella and less severe itchiness and pain. The recommended dose of oral acyclovir was 20 mg per kg four times a day for five days (with a maximum of 800 mg per dose) in children and 800 mg five times a day in adults. Exactly who should receive acyclovir is controversial because the drug is relatively expensive—$20 for a five-day course in a 10-kg child—and of modest clinical benefit. Immunocompromised patients and patients with notable clinical disease, such as varicella pneumonia, should not be treated with oral acyclovir but should be admitted to a hospital and given intravenous acyclovir.

Laboratory Test

The US Food and Drug Administration has recently approved a latex agglutination test that is rapid, cheap, simple, and accurate in evaluating immunity to varicella, especially in pregnant women who have had exposure to the virus and who do not know if they ever had the disease. This test is highly successful in identifying antibodies to the virus and will be available in most hospital laboratories shortly. This test will supplement or replace the currently available tests, fluorescent antibody against membrane antigens, which are costly, labor-intensive, and require a high degree of skill.

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Human Genome Project

THE HUMAN GENOME PROJECT is the largest organized cooperative effort ever to be undertaken in the biologic sciences. The goal is to determine the DNA sequence of the entire human genetic program—to map and sequence every gene in the body. The complement of DNA in each cell of the body comprises about 50,000 to 100,000 functional units or genes encoded by an alphabet that has only four letters: A, adenine; C, cytosine; G, guanine; and T, thymine. About 3×10^9 letters, however, are strung together. Thus, if the linear sequence of our DNA were printed out, it would require the equivalent of nearly 100 volumes of a telephone directory to display this information. Our current understanding is that only 3% to 5% of this DNA actually codes for functional proteins that appear in some cell of the body at some stage of development. The purpose of much of the remaining DNA is as yet unclear.

Many scientific and technical problems must be overcome before the goals of the project are realized. Methods to locate individual functional genes by "mapping" techniques must be refined and made efficient, and economical procedures for sequencing must be developed. Given likely improvements in such technology, this program is feasible, but only at great cost and only with many participating laboratories cooperating in the effort.

One of the first areas affected will be an enhanced ability to diagnose and treat genetic diseases. Recent discoveries about the molecular basis of common pediatric conditions such as cystic fibrosis, Duchenne muscular dystrophy, retinoblastoma, myotonic dystrophy, and the fragile X syndrome, to name but a few, are among the early disorders to yield their secrets. We have already seen the development of rapid DNA-based tests that facilitate accurate prognostic information for these and other diseases. With more than 4,000 distinct genetic diseases known, there is a long way to go. Perhaps more important, completion of the project will allow us to identify innumerable heretofore-unknown genes and permit us to study their functions and roles in normal and pathologic processes.

Mapping the complete human DNA sequence is not an end in itself, but rather a tool to be used in concomitant and subsequent investigations. Understanding which of our genes is active and involved in development processes, oncogenesis, the response to infection, and autoimmunity will permit the design of rational interventional strategies to deal with birth defects, cancer, and many other disorders both inherited and acquired. Although the biotechnology revolution has already produced a host of new therapeutics, this number can be expected to increase by orders of magnitude using this new genomic information.

Another likely benefit of research is in the area of disease prevention. Advances in human genetics are likely to identify inherited risk factors for disorders that appear in adult life following exposure to environmental insults. A knowledge of which persons have an increased chance of common diseases of adulthood developing may permit targeted interventions that prevent or ameliorate such situations.

There are many ethical and social issues raised by the human genome project. These include concerns of genetic discrimination, the lack of availability of health care insurance for people at high risk, confidentiality of testing information, and the allocation of scarce resources. It seems certain, however, that much good will come from this work. Pediatrics will be among the medical specialties to benefit earliest and most prominently.

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Sleep Positioning and the Sudden Infant Death Syndrome

INFANTS' SLEEP POSITION has been a topic of little interest until recently. Advice from physicians and nurses to parents about sleep position has been based on scant data and thought to be of minimal clinical importance. The sudden infant death syndrome (SIDS) is the sudden, unexpected death of an apparently healthy infant that remains unexplained after a complete postmortem investigation, including an autopsy, examination of the death scene, and review of the case history.

Over the past 15 years, published reports have associated prone sleeping with an increased incidence of SIDS. Based on these reports, physicians in the United Kingdom and New Zealand have recommended that all healthy infants should sleep in a nonprone position. The question that practicing physicians and nurses in the United States must ask is, "How good are the data that prone sleeping is associated with SIDS?"

The American Academy of Pediatrics recently convened a task force to answer this question. The task force concluded that the data are convincing and furthermore stated that "no reports showed an advantage to the prone position with regard to SIDS incidence and there are no data proving, or even strongly suggesting, that sleeping in the lateral or supine position is harmful to the normal infant."

Since 1965, 25 studies have been published that considered the relationship between sleep position and SIDS. Most of these studies involved retrospective interviews after an infant died of SIDS or prospective interviews with parents of children at high risk of SIDS. Most of these studies had methodologic limitations and were conducted in countries with infant care practices and other SIDS risk factors that differ from those in the United States. Only 11 of these 25 studies used acceptable criteria for the definition of SIDS, included adequate control groups, and produced sufficient data.

These 11 studies were grouped into 3 study designs: studies examining the "usual sleep position" (7), studies examining how the infant was "last put down" before death (3), and studies asking how the infant was "found" after death (1). All of these studies showed an increased incidence of SIDS in infants who slept in the prone position, with statistical significance in all but 1 of the 11 studies. Hypotheses to explain why an infant who sleeps prone is more likely to die of SIDS include oropharyngeal obstruction, response to hypercapnia and hypoxemia, soft porous sleeping surfaces, effects on cerebral blood flow, and overheating.

There is no evidence that in healthy newborns supine or side positioning increases the incidence of aspiration or any

other serious complication. On the contrary, well-designed studies have shown that children with special needs, such as premature infants with respiratory compromise, infants with symptomatic gastroesophageal reflux, and infants with upper airway problems such as Robin's anomalad, fare better sleeping prone.

It must be emphasized to parents of healthy newborns that although associated with SIDS, prone sleeping does not cause it; and infants who insist on sleeping prone still have a low "actual risk" of SIDS. Most important, research must continue in this area so we may discern the variables that lead to this association or to disprove this association.

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Management of Intracranial and Spinal Cord Vascular Lesions in Children

MANY ADVANCES HAVE occurred in the past five years in the management of intracranial and spinal cord vascular lesions in children. These advances include improved diagnostic abilities (magnetic resonance imaging [MRI]), new interventional neuroradiologic techniques, and focused radiation therapy (radiosurgery).

The introduction of MRI has revealed vascular lesions not seen on angiography, such as cryptic vascular malformations, also known as angiographically occult vascular malformations. These lesions have been diagnosed with increased frequency because of their characteristic appearance on MRI of the mixed-signal intensity of recent and remote hemorrhage. Cryptic vascular malformations commonly produce seizures, repetitive bleeding, neurologic deficits, and, in some cases, death. The pathologic features of these malformations continue to be debated. Most can and should be removed by modern microsurgical techniques. The reported morbidity of this surgical procedure has been low even when it involves the brain stem or the motor or language cortex.

The diagnosis and management of a second disease process, intracerebral and spinal cord arteriovenous malformations, have undergone dramatic improvement. Magnetic resonance imaging can detect and localize them, often before catastrophic hemorrhages have occurred. Interventional neuroradiologic and surgical techniques can obliterate these high-risk abnormalities. Preoperative embolization in conjunction with intraoperative angiography has made "unresectable" arteriovenous malformations surgically excisable with minimal morbidity and mortality. For children with these lesions and a seizure disorder, the malformation is surgically excised in conjunction with intraoperative motor mapping and electrocorticography to remove the seizure focus. Radiosurgery has also been successfully used in children who have arteriovenous malformations in critical areas of the brain or who are thought to carry a substantial neurologic risk with surgical treatment. Both the gamma knife and linear accelerator have shown effectiveness in treating small (less than 3 cm) arteriovenous malformations. These lesions are progressively obliterated over two to three years after radiosurgery. The incidence of transient or permanent radiation damage is in the range of 2% to 4%, but complete obliteration occurs in more than 80%. To date, there is no evidence that secondary tumors are induced as the result of radiosurgery.

Combined arterial and transvenous interventional neuroradiologic techniques have dramatically improved the prognosis for infants born with a vein of Galen malformation associated with high-output congestive heart failure, previously a fatal condition.

Despite these many advances, some rare vascular malformations are not amenable to current neurosurgical therapies. These include arteriovenous malformations that diffusely permeate the brain stem and giant vascular malformations that involve an entire hemisphere. With a better understanding of the pathophysiology of vascular lesions and continued improved technologies, even these rare lesions may soon be corrected.

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Laparoscopic Surgery

LAPAROSCOPIC SURGERY is gaining acceptance among pediatric surgeons and their patients around the world. Appendectomy, cholecystectomy, Nissen fundoplication for gastroesophageal reflux, herniorrhaphy, colectomy, vagotomy, and splenectomy have all been done laparoscopically. In addition, the laparoscope can be used in children to evaluate abdominal pain of unknown cause, for treating undescended testes, and for doing biopsies of lymph nodes and tumor.

To do a laparoscopic procedure, the child must be under general anesthesia with the stomach and bladder decompressed. A retractable blunt-tipped needle is inserted through a stab wound just inside the umbilicus, and a cannula is inserted into the abdomen to fill it with carbon dioxide to a pressure of 10 to 12 torr. The procedure is then done. Laparoscopic procedures have been done on infants weighing as little as 2 kg.

Laparoscopy offers the benefits to children of decreased perioperative pain, shorter hospital stays, and an earlier return to unrestricted activity including sports. Postoperative ileus is less common after laparoscopy than after conventional operations. The decrease in length of hospital stay, however, is less pronouced in children than in adults. Children are known to recover quickly after conventional operations, and many of these procedures are generally done on an outpatient basis. The average decrease in hospital stay after a laparoscopic procedure compared with an abdominal operation is one day for an appendectomy and two days after a cholecystectomy.

Possible complications include visceral injury during trocar introduction and difficulty with ventilation when patients are insufflated with too great a pressure. Carbon dioxide absorption also poses the possibility of hypercapnia with

carbon dioxide narcosis and respiratory acidosis. With experience, tissue injury and major hemorrhage are rare. Many of the complications seen in adult laparoscopic procedures result from the use of lasers or monopolar electrocautery. As safer bipolar instruments are introduced, the incidence of these types of injuries will decline.

Whether a surgeon chooses to do a procedure laparoscopically depends to a large extent on experience, training, and the long-term outcome of some of the procedures. For example, the incidence for the recurrence of inguinal hernia and gastroesophageal reflux following fundoplication could be greater than that from conventional repair.

Thus far, the results of laparoscopic operations in children are encouraging. As the instrumentation improves, surgeons will gain experience with more complicated reconstructive procedures. Laparoscopic surgery will be applied more frequently in children and in many cases will obviate a more extensive surgical procedure and prolonged hospital stay.

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Depot Levonorgestrel (Norplant) Use in Teenagers

NORPLANT (long-acting depot levonorgestrel) is well established as a contraceptive for women. It is especially well suited for women who wish long-term contraception, substantial birth spacing, a method independent of self- or partner participation (compliance) or timing of coitus, and avoidance of other contraceptives that have caused important side effects (such as intrauterine devices or estrogen).

Although there is no published information on the use of Norplant in teenagers, an adolescent service has used it in hundreds of teenagers.

Norplant consists of six flexible silastic capsules containing the hormone levonorgestrel. These capsules are inserted subdermally into the underside of a woman's upper arm through a surgical incision, usually in an outpatient setting. Norplant inhibits ovulation and thickens cervical mucus, thus making it impenetrable to sperm.

Levonorgestrel has been used widely in both progestin-only and in combined oral contraceptive pills. Now with the delivery method changing from oral to implantable, Norplant has become the most effective, reversible, long-term contraceptive available. It does not rely on patient compliance and therefore virtually eliminates all pregnancies for five years. Every year, one of every ten teenaged girls between ages 15 and 19 becomes pregnant, resulting in more than a million pregnancies in this age group in 1990 alone. Thus, based on the high number of unintended teenaged pregnancies in the United States, many of which are due to a lack of compliance, Norplant may prove to be the ideal contraceptive for some teens.

Norplant is by no means a panacea. Eight of ten women using Norplant report heavy, irregular bleeding. This common side effect is the primary reason for discontinuing its use. In addition, public health concerns have surfaced regarding the potential for a decrease in the use of condoms with Norplant and thus an increase in the risk of sexually transmitted diseases, including human immunodeficiency virus infection and hepatitis B.

Ethical issues have been expressed regarding Norplant's possible use in a coercive manner by parents or health care professionals or by its use in "targeted groups." Health care professionals must be vigilant to make sure this does not occur. Norplant is but another contraceptive choice and should be offered to teenagers as one of many options available to them. The final choice must be their own.

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Alerts, Notices, and Case Reports

Successful Combined Liver and Small Intestine Transplantation for Short-Gut Syndrome and Liver Failure

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SMALL INTESTINE TRANSPLANTATION has been a subject of intense research since the pioneering studies by Lillehei and co-workers in 1959.[1] Difficulties in controlling sepsis, rejection, and graft-versus-host disease largely confined small intestine transplantation to research laboratories until recently. With several decades of research, the successful use of cyclosporine in solid organ transplantation, and the discovery of newer immunosuppressive agents, small intestine transplantation has emerged as a treatment option in selected patients.[2] We report herein the first successful human combined liver and small intestine transplantation in the western United States.

Report of a Case

The patient, a 20-year-old man, was previously healthy until June 1989 when he sustained a midabdominal stab wound that involved his superior mesenteric artery and vein. The patient underwent emergent laparotomy with primary repair of both vessels. Within 24 hours, peritonitis developed, and he underwent a second laparotomy in which ischemia of the right colon secondary to a thromboembolus was discovered, and a right hemicolectomy was done. After the operation intestinal angina developed, and about three weeks later an episode of gastrointestinal bleeding ensued. A visceral angiogram was obtained and revealed a thrombosed superior mesenteric artery and active bleeding from the proximal jejunum. The small intestine was supplied by collaterals from the gastroduodenal artery. Surgical attempts to control the ongoing hemorrhage resulted in the loss of the entire small intestine from the third portion of the duodenum to the transverse colon. He underwent enterectomy with the remaining viable intestine anastomosed primarily. His immediate postoperative course was stormy, requiring several reoperations for sepsis and peritonitis, but he was eventually discharged from the hospital on total parenteral nutrition (TPN). The anastomosis of his gastrointestinal tract is illustrated in Figure 1.

From July 1989 the patient was maintained on TPN and had complications including several episodes of catheter sepsis, left subclavian-axillary venous thrombosis, and cholestasis leading to liver failure. About a year after the patient started TPN, early signs of liver dysfunction developed that had progressed to chronic liver failure by November 1990. A liver biopsy at that time revealed cholestatic liver failure consistent with chronic TPN administration. The patient's liver failure was progressive, and on admission to UCLA Medical Center (Los Angeles, California) for treatment and transplant evaluation on September 19, 1991, his liver function test values included the following: total serum bilirubin, 416 μmol per liter (24.3 mg per dl; range, 5 to 21); aspartate aminotransferase, 235 units per liter (range, 5 to 40); alanine aminotransferase, 200 units per liter (range, 5 to 50); alkaline phosphatase, 111 units per liter (range, 30 to 105); al-

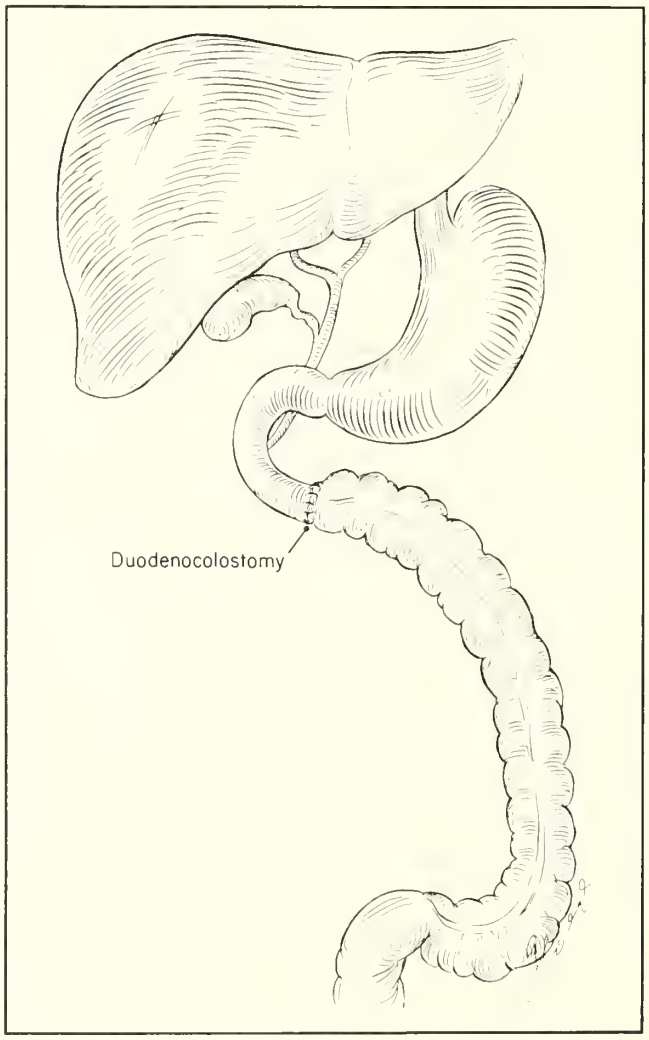

Figure 1.—The schematic drawing represents the patient's remaining intestine after his initial injury and operations. Note that the second duodenum is anastomosed primarily to the transverse colon.

(Busuttil RW, Farmer DG, Shaked A, et al: Successful combined liver and small intestine transplantation for short-gut syndrome and liver failure. West J Med 1993 Feb; 158:184-188)

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bumin, 30 grams per liter (3.0 grams per dl; range, 40 to 52); and prothrombin time, 2 seconds above normal. After an extensive preoperative evaluation by a multidisciplinary transplant team, the patient was accepted as a candidate for combined liver and small intestine transplantation.

A size-matched, ABO-identical donor who died of a massive intracerebral hemorrhage was located on November 11, 1991. The HLA phenotypes were mismatched at all loci and were A1A3, B7B8, C-C-, DR3/DR6 in the donor and A2A28, B51B-, C1C6, DR1/DR15 in the recipient. The donor bowel was prepared preoperatively with mechanical cleansing and enteral antibiotic solution. The liver and small intestine were procured en bloc in an operation that lasted 3.5 hours using a modified technique of that described elsewhere.[3,4] The graft was flushed with University of Wisconsin solution and stored for a total of 4 hours 44 minutes.

A total hepatectomy was done and the patient's colon divided approximately 10 cm distal to the previous duodenocolonic anastomosis. The graft was placed en bloc in the orthotopic position in the recipient. The arterial supply was obtained from the supraceliac abdominal aorta using an allogeneic iliac bifurcation graft to the hepatic artery and superior mesenteric artery of the graft (Figure 2). The venous outflow was through the suprahepatic vena cava, and the infrahepatic vena cava was anastomosed in an end-to-end manner. The patient's portal venous circulation was restored to the liver graft by an end-to-side anastomosis to the stump of the donor splenic vein. Intestinal continuity was achieved with an end-to-side colojejunostomy proximally and an end-to-side ileocolostomy distally (Figure 3). The distal ileum was vented to the anterior abdominal wall as a Brooke ileostomy, the proximal jejunum was used to create a Roux-en-Y choledochojejunostomy, and a Stamm gastrostomy was done. In total, the recipient operation lasted about 12 hours.

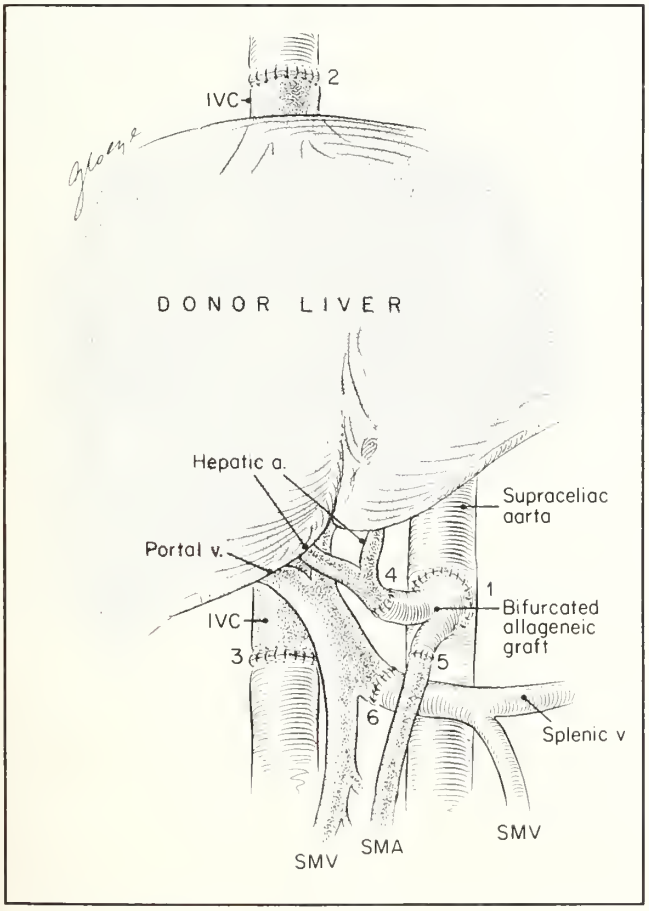

Figure 2.—The schematic drawing shows the vascular connections used for the combined liver-small intestine transplant. A bifurcation graft is represented off the supraceliac aorta that is anastomosed to the superior mesenteric artery (SMA) and hepatic artery of the graft. 1 = Allogeneic bifurcation graft to supraceliac aorta anastomosis, 2 = suprahepatic infrahepatic vena cava (IVC), 3 = IVC anastomosis, 4 = limb of bifurcation graft to hepatic artery anastomosis, 5 = limb of bifurcation graft to superior mesenteric artery anastomosis, 6 = recipient portal vein to donor splenic vein anastomosis, SMV = superior mesenteric vein

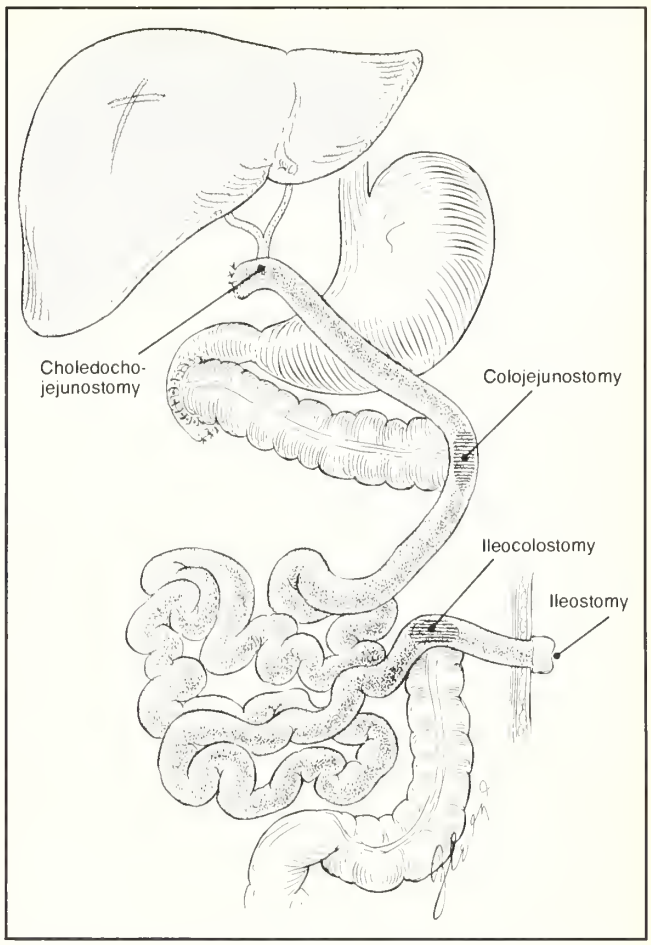

Figure 3.—The schematic drawing shows the gastrointestinal connections between the donor intestine (hatched) and remaining recipient intestine. Biliary drainage was achieved with a Roux-en-Y choledochojejunostomy. The transplanted intestine was placed in continuity using a proximal end-to-side cholejejunostomy and a distal end-to-side ileocolostomy. The distal transplanted intestine was vented to the anterior abdominal wall as an ileostomy.

After the operation the patient was extubated within 24 hours and was maintained in the intensive care unit for the first nine postoperative days. His initial immunosuppressive regimen consisted of cyclosporine, monoclonal anti-T3 antibody (OKT3), methylprednisolone sodium succinate, and azathioprine. Graft function was closely monitored using serum biochemical tests, liver biopsies, small intestine biopsies, endoscopy, gastrointestinal radiography, lidofenin (HIDA; iminodiacetic acid) scans, and gastrointestinal permeability studies. Bowel decontamination was attempted daily using an antibiotic solution of gentamicin sulfate, colistin (polymyxin E) sulfate, and nystatin.

The patient had a single episode of graft rejection involving both the liver and small intestine on postoperative day 26.

The rejection episode was confirmed by endoscopy, radiographically, and histologically (Figures 4 and 5). The initial treatment of the rejection episode included high doses of steroids and antibiotic prophylaxis. After two days without signs of improvement and when graft loss appeared imminent, the primary immunosuppressant was changed from cyclosporine to FK 506. Clinical improvement was achieved

Figure 4.—An upper gastrointestinal study using diatrizoate meglumine (Gastrografin) for contrast was obtained at the time of clinical and histologic rejection (postoperative day 26). Note the ulcerated appearance of the small intestine.

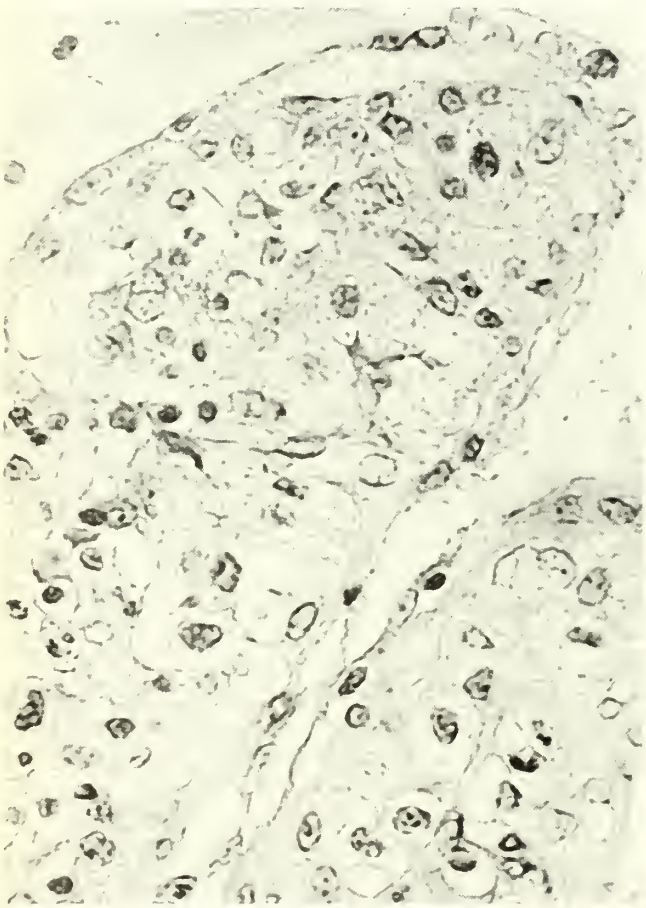

Figure 5.—The photomicrograph represents small intestine that was obtained by biopsy on postoperative day 26. The specimen was fixed in Bouin's solution, stained with hematoxylin and eosin, and magnified 40×. The intestinal villus shows a total loss of enterocytes as well as lymphocytic infiltrate consistent with rejection.

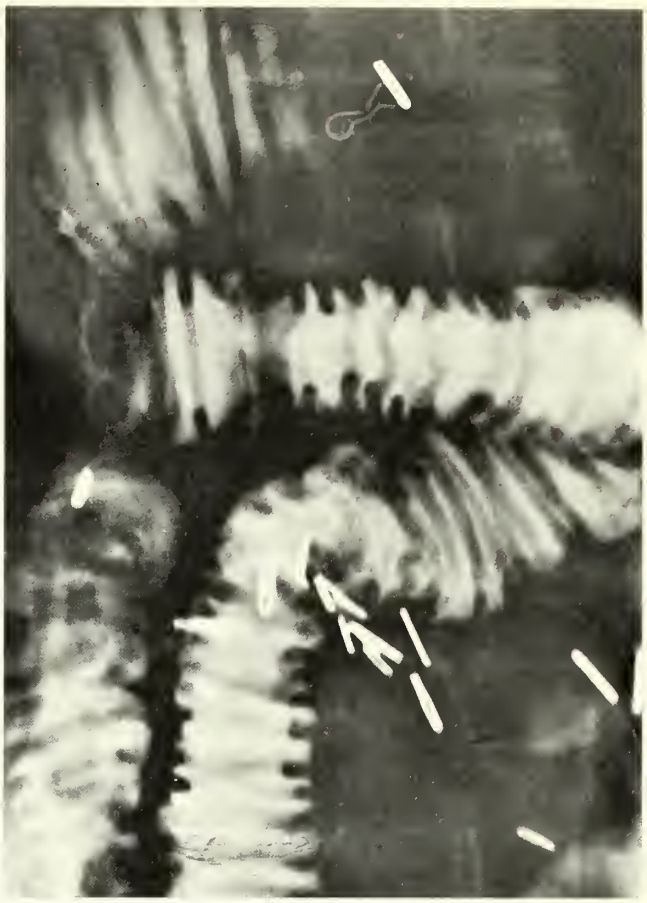

Figure 6.—An upper gastrointestinal contrast using diatrizoate meglumine (Gastrografin) for contrast was obtained on postoperative day 37. Note the normal appearance of the small intestine mucosa, in contrast to that on Figure 4.

within two days, and follow-up biopsies, endoscopy, and gastrointestinal radiography showed complete resolution of the rejection episode (Figures 6 and 7).

The patient also had an episode of fungemia requiring intravenous amphotericin B therapy beginning on postoperative day 8. Subsequent cultures of blood, sputum, and urine specimens were negative, but the transplanted intestine remains colonized with yeast. Other postoperative complications included a persistent gastroparesis refractory to medical management. This problem has been circumvented by placing a transgastrostomy feeding jejunostomy tube. A gastrocutaneous fistula also developed on postoperative day 46, thought to be related to the gastrostomy tube and gastroparesis. This fistula closed down by postoperative day 75.

The patient was maintained initially on TPN until postoperative intestinal function resumed. Jejunostomy tube feeds were initiated on day 16, and a gradual weaning off TPN onto enteral feedings was initiated shortly thereafter. By day 34, the patient's total nutritional needs were supported by enteral feeding. The patient was discharged from the hospital on day 79 with a functioning liver and small intestine allograft.

Discussion

The short-gut syndrome is a clinical disorder that results from several pathologic and traumatic conditions.[5] Total parenteral nutrition provides life-sustaining nutrition for this condition that would otherwise be fatal. This treatment is subject to limitations and complications that can include life-

TABLE 1.—*World Experience in Small Intestine Transplantation Since 1987*

Transplantation Center	*Small Bowel Transplant Patients, No./Survived**	*Liver-Small Bowel Transplant Patients, No./Survived**	*Total Patients, No./Survived**	*Source*
Paris, France	7/5	0/0	7/5	Schroeder et al, 1990[15]
Kiel, Germany	3/1	0/0	3/1	Schroeder et al, 1990[15]
Sweden	1/0	0/0	1/0	Schroeder et al, 1990[15]
London, Ontario	1/1	3/2	4/3	Grant et al, 1990[16]
Madison, Wis	0/0	1/0	1/0	D'Alessandro, 1992†
Omaha, Neb	0/0	3/1	3/1	Langnas, 1992‡
Pittsburgh, Pa	5/5	8/7	13/10	Reyes, 1992§
Los Angeles, Calif	0/0	1/1	1/1	This report
Total	17/12	16/11	33/23	

*Number of patients undergoing transplant versus number of patients alive with transplanted graft.
†A. M. D'Alessandro, MD, Department of Surgery, University of Wisconsin School of Medicine, Madison, oral communication, January 1992.
‡A. Langnas, MD, Division of Transplantation, University of Nebraska Medical Center, oral communication, January 1992.
§J. Reyes, MD, Department of Transplantation, University Health Center of Pittsburgh, oral communication, January 1992.

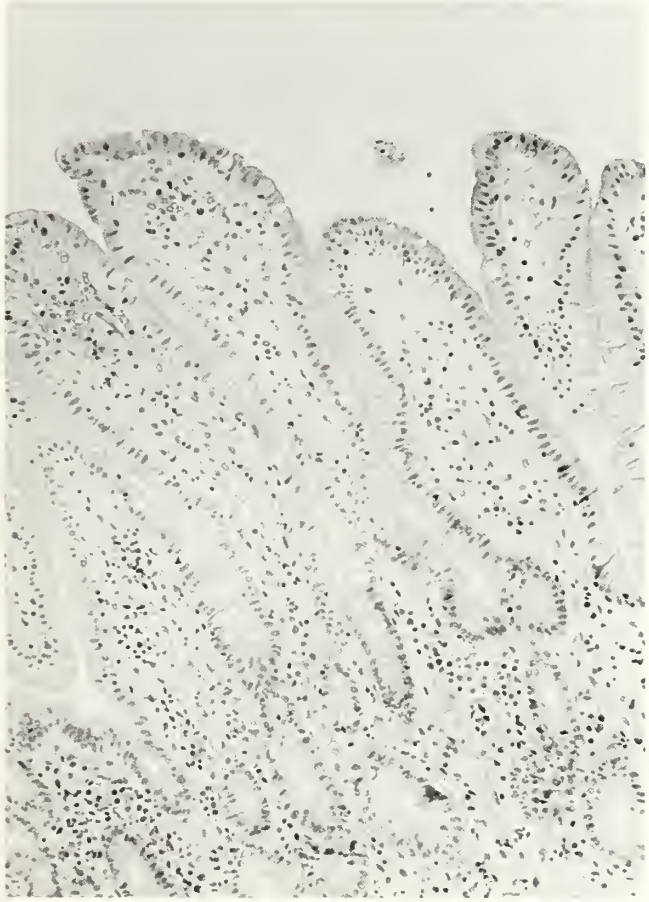

Figure 7.—The photomicrograph shows transplanted small intestine from a representative biopsy specimen that was obtained on postoperative day 35, fixed in Bouin's solution, and stained with hematoxylin and eosin (original magnification × 40). Note the normal-appearing mucosal architecture.

style limitations, psychosocial problems, vascular access problems, catheter-related sepsis, cholelithiasis, cholestasis, liver failure, and death.[6-8]

Until recently, no alternative therapies for patients with the short-gut syndrome have had practical application. Small intestine transplantation has provided a theoretic treatment alternative for these patients, but the initial attempts in the 1960s and 1970s were uniformly unsuccessful.[2,9] With advances in immunosuppressive agents and antimicrobial agents, the major barriers to small intestine transplantation are being addressed in the laboratory.[2,10-14] The laboratory success has led to renewed attempts at human small intestine transplantation (Table 1).[15,16] Since 1987, 33 small intestine transplantations have been attempted worldwide. Of these, 17 are isolated small intestine transplants and 16 are combined liver and small intestine. The numbers listed in Table 1 represent a considerable advance from the early attempts of the 1960s and 1970s.

The problems encountered with this patient are typical of those encountered with transplantation of the small intestine. Rejection is a major barrier to small intestine transplantation because of the antigenicity of the small intestine allograft. Cyclosporine has been used with success in human transplant attempts in London, Ontario, Canada,[16] Omaha, Nebraska (A. Langnas, MD, Division of Transplantation, University of Nebraska Medical Center, oral communication, January 1992), Paris, France,[15] and Kiel, Germany.[15] In our patient, cyclosporine proved ineffective at suppressing rejection, and the regimen had to be changed to FK 506.[17]

It is always difficult to reduce a surgical intervention such as this to purely monetary terms, especially in light of the tremendously positive effect it has had on this patient's life. We estimate the cost for the acute hospital care and transplantation to be about $600,000. This is considerably more expensive than an uncomplicated liver transplantation at our institution but is well within the range for a complicated liver transplantation requiring prolonged hospital care. In addition, this represents our first transplantation of this nature, and, as experience is accumulated, we estimate the cost will decrease. This has proved to be the case with liver transplantation at UCLA in which the cost of clinical services has decreased by 32% over the past two years.

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Occult Kawasaki Syndrome With Giant Coronary Artery Aneurysms

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THE KAWASAKI SYNDROME is an acute febrile illness of unknown cause. The diagnosis is considered established by finding five of the following six clinical criteria:

- Fever for longer than five days;
- Conjunctival injection;
- Oral and mucous membrane changes;
- Edema, erythema, and desquamation of the extremities;
- A polymorphous rash; and
- Nonsuppurative lymphadenopathy.[1]

The strict application of these criteria may result in the failure to recognize some cases of atypical Kawasaki syndrome in patients who may have fewer than five of the six criteria. Identification of these cases, both typical and atypical, is important because of the well-documented risk of coronary artery aneurysm with its attendant morbidity and mortality.[2] We report the case of a child in whom five of the six criteria for the diagnosis of Kawasaki syndrome were eventually met. The child's clinical presentation was unusual, and the diagnosis was unsuspected until giant coronary artery aneurysms were discovered early in the disease course. This case illustrates diagnostic difficulties in a disease process that carries high potential morbidity and that requires early intervention.

(Hinson RM, Schofield TD, French J, Stevenson JG, Stewart D, Kinney JB Jr: Occult Kawasaki syndrome with giant coronary artery aneurysms. West J Med 1993 Feb; 158:188-191)

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Report of a Case

The patient, a 7-year-old boy, presented to the pediatric clinic five days before admission with an abrupt onset of right-sided neck tenderness. On evaluation he was noted to have a moderately erythematous posterior pharynx and a 1- by 1.5-cm tender, nonfluctuant right anterior cervical lymph node. There had been no fever. A diagnosis of pharyngitis and lymphadenitis was made, and a regimen of amoxicillin and clavulanate potassium was started. Three days before admission, the patient had the sudden occurrence of fever, watery diarrhea, malaise, and a yellowish penile discharge. A rash appeared in the groin and buttocks area and spread to the proximal lower extremities. The amoxicillin-clavulanate combination was thought to be the cause of the rash, and it was discontinued. The cervical lymphadenitis progressed, so the patient was admitted on the fifth day of his illness for intravenous antibiotic therapy.

The patient's medical history was pertinent only for a perirectal abscess at 9 months of age. He had never had a prolonged febrile illness.

On admission, the patient had a temperature of 38.9°C (102°F), a heart rate of 120 beats per minute, a respiratory rate of 26 per minute, and a blood pressure of 103/57 mm of mercury. He had a pronounced torticollis guarding his tender cervical lymph node. Both conjunctivae were equivocally injected, and his pharynx was erythematous, in both cases without exudate. There was a markedly tender 2- by 4-cm right anterior cervical lymph node. No other lymphadenopathy was present. The results of a cardiopulmonary examination were unremarkable. The abdomen was normal. Distal extremities were without edema or inflammation. His genitals were unremarkable except for an erythematous meatus showing minimal yellowish discharge. A diffuse erythematous macular rash with occasional target lesions was present over the trunk and proximal lower extremities. His neurologic system was within normal limits.

Initial laboratory studies revealed a leukocyte count of 15.6×10^9 per liter (15,600 per μl), hemoglobin 136 grams per liter (13.6 grams per dl), hematocrit 0.39 (38.5%), and a platelet count of 520×10^9 per liter (520,000 per μl). Electrolytes were normal. An erythrocyte sedimentation rate was 123 mm per hour. A urinalysis was remarkable for pyuria (10 leukocytes per high-power field). Cultures of blood, urine, and urethral specimens were negative. An initial chest x-ray film was normal (Figure 1-A).

The patient was treated with intravenous clindamycin. Within 48 hours of the institution of therapy, he had a dramatic resolution of his right cervical tenderness. There were also resolution of his conjunctivitis and a substantial reduction of his rash.

At this point in his illness, it appeared that this child had a resolving cervical lymphadenitis. The defervescence and improvement in the lymph node tenderness seemed to support this diagnosis. A sterile penile discharge was not consistent with cervical adenitis, however; it suggested systemic in-

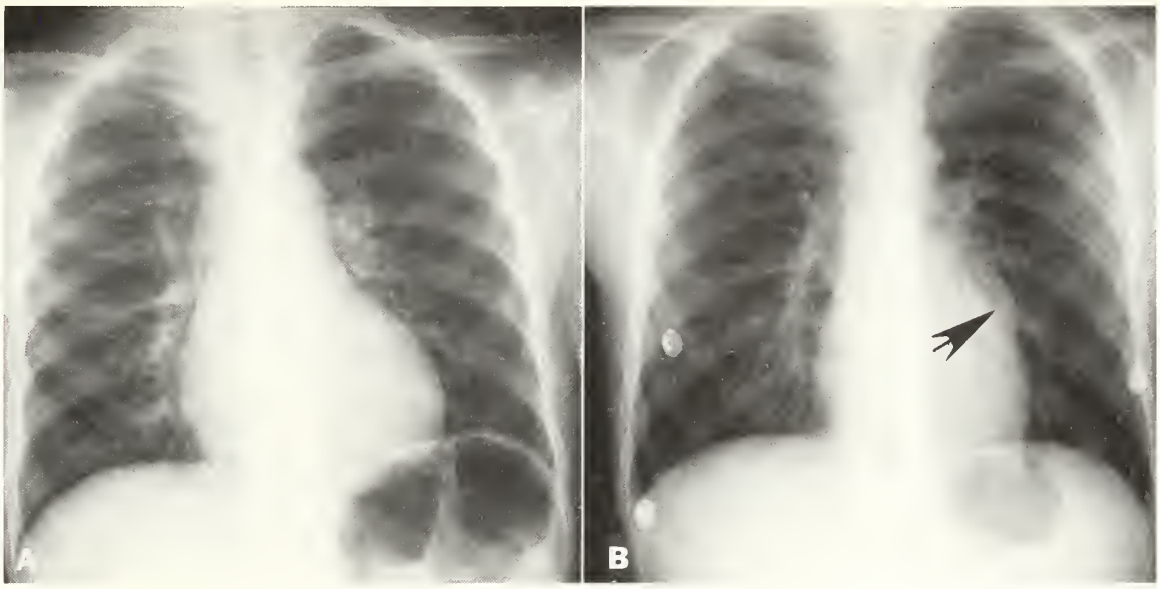

Figure 1.—**A,** An initial chest x-ray film on admission to hospital at day 5 of illness shows normal cardiac size and contour and unremarkable lung fields. **B,** A chest x-ray film taken at 7 weeks of illness shows distinct change in the contour of the left heart border **(arrow),** in the location of a large aneurysm in the left anterior descending coronary artery.

flammation. Among the inflammatory disorders considered was the Kawasaki syndrome. An echocardiogram was obtained on the eighth day after admission (13th day of illness) and showed involvement of both the right and left coronary arteries. The right coronary artery had a fusiform aneurysm 1.3 cm in diameter with a thrombus noted in the lumen. The left coronary artery had extensive involvement. The left anterior descending coronary artery had a 1.7- by 2.9-cm aneurysm. A clot could also be visualized within this aneurysm (Figure 2).

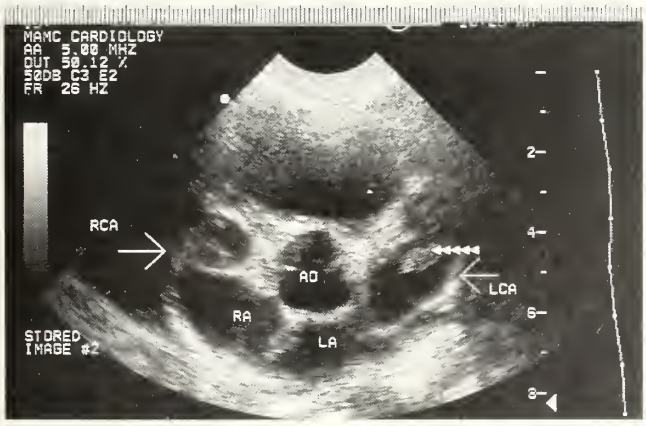

Figure 2.—An echocardiogram was taken on the 13th day of illness. This is a short-axis image at the level of the aortic valve **(AO),** with the right atrium **(RA)** and left atrium **(LA)** shown. There is a large aneurysm of the left coronary artery **(LCA),** with thrombus visible within **(chain of arrows).** The right coronary artery **(RCA)** is also aneurysmally dilated, with thrombus present.

The patient was initially treated with high doses of aspirin and urokinase, followed by heparin therapy for six weeks, with a gradual resolution of the identified clots. The aneurysms increased in size to the point that a change in the cardiac contour was noted on chest x-ray film (Figure 1-B). The patient was asymptomatic with a normal electrocardiogram, however, and was discharged on a regimen of warfarin sodium (Coumadin) and low doses of aspirin.

Serial echocardiograms over a period of four months showed a continuing increase in the size of the aneurysms, although they remained free of clot. The patient was subsequently taken to angiography and studied using a standard retrograde aortic technique. Many angiographic views were used to demonstrate the coronary artery abnormalities (Figures 3 through 6).

The left anterior descending coronary artery had two aneurysms (Figures 3 and 6). The proximal lesion was huge, exceeding 4 cm. A second smaller lesion was seen in the distal left anterior descending. A large aneurysm was found in the circumflex coronary artery (Figures 4 and 6). The right coronary had a long (more than 4 cm) severely dilated lesion (Figures 5 and 6). No thrombus was identified in the coronary system.

The patient was asymptomatic on aspirin and warfarin therapy at 16 months into his illness. Serial echocardiograms showed enlarging aneurysms. Cardiac surgical consultation was obtained. Resection of the massive aneurysms was thought not to be feasible, and coronary artery bypass would not affect the capacity for thrombus formation; thus, it was elected to continue the current medical management.

At 17 months of illness during an evaluation for abdominal pain, electrocardiographic changes were noted consistent with myocardial infarction. The infarct occurred despite aspirin and warfarin therapy and with prothrombin times consistently 18 to 21 seconds. A resting thallium scan showed substantial abnormality of the inferior septum and all apical aspects. Digoxin and afterload reduction therapy was begun, and he remains asymptomatic on this therapy.

Discussion

Since the first description more than two decades ago,[1] the Kawasaki syndrome has been an increasingly recognized cause of disease in the United States.[3] The development of coronary artery aneurysms is the major cause of serious morbidity and mortality in these patients.[4] Coronary artery aneurysms develop in about 10% to 20% of patients.[4] Dilation of the coronary arteries may resolve over one to two years in

about half of affected patients.[5,6] Kato and co-workers have noted, however, that giant aneurysms, greater than 8 mm in maximal diameter, have tended to have a lengthy course.[6]

This case demonstrates the protean character of the Kawasaki syndrome. Even in retrospect the diagnosis was obscure. The initial isolated lymphadenitis without concurrent fever, the apparent antibiotic rash and absence of edema, erythema, or desquamation of the extremities, and the urethritis and diarrhea were all misleading. The conjunctivitis was equivocal, and mucous membrane changes were confined to the pharynx. The rapidity in development of large aneurysms in this patient who was not severely ill is notable. We can find no reports in the English-language literature of coronary aneurysms approaching this size, although Travaline and colleagues reported the case of a patient with moderately large aneurysms and myocardial infarction requiring a cardiac transplantation.[7] Our patient's echocardiogram done only 13 days after the onset of symptoms again shows the fulminant course this disease may take.[8]

The evolution of this child's disease process is of concern as thrombus formed despite what was considered adequate therapy for preventing thrombus. The role of medical versus surgical treatment in this syndrome with giant coronary artery aneurysms is unclear. Tatara and Kusakawa have noted that aggressive antiplatelet treatment is often not successful in preventing thrombus formation.[9] This case demonstrates that the addition of warfarin did not prevent thrombus formation. Our experience suggests a reevaluation is needed of the adequacy of antithrombolytic therapy in Kawasaki syndrome with giant coronary artery aneurysms. Additional deterioration in this patient will mandate an active consideration of cardiac transplantation.

Early detection is vital if therapy is to alter the development of coronary artery aneurysms. Early treatment with intravenous immunoglobulin and aspirin is associated with a pronounced decrease in the prevalence of coronary artery aneurysm formation, and giant aneurysms may be virtually eliminated.[10] Our recommendation is that any child with

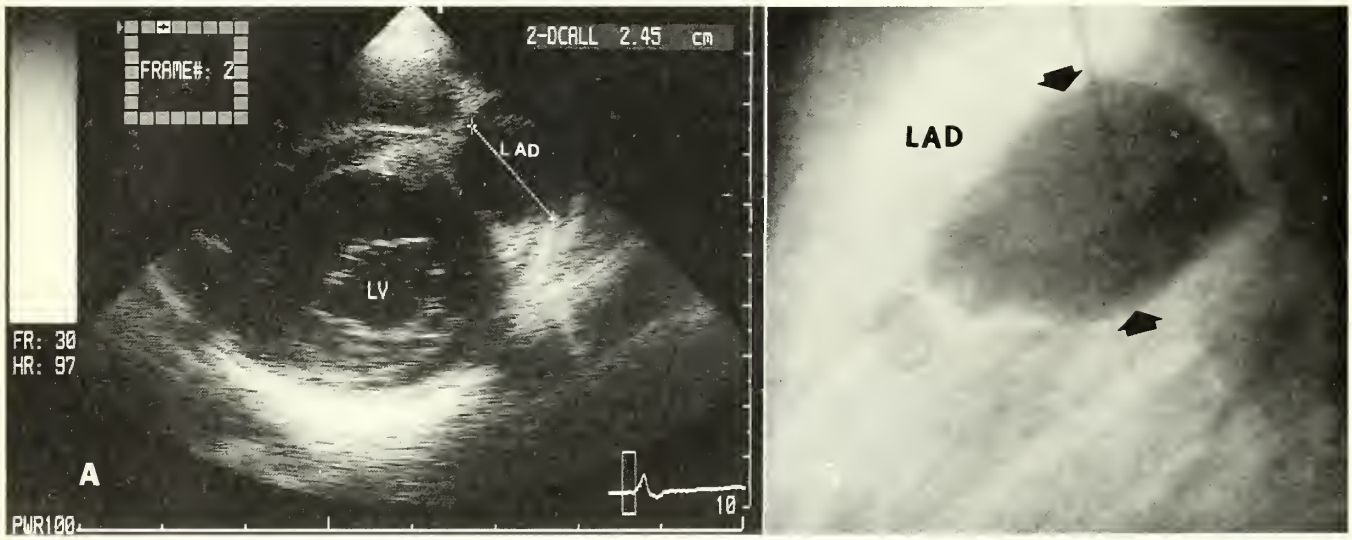

Figure 3.—A, A short-axis echocardiographic image of the left ventricle (LV) 6 months into illness shows a large aneurysm of the left anterior descending (LAD) artery. The aneurysm in this plane measures 2.45 cm in diameter. B, A cineangiographic frame of the selective LAD arteriogram shows the large aneurysm (arrows) with a smaller aneurysm to the left and inferiorly. Catheter size is 4.5 F.

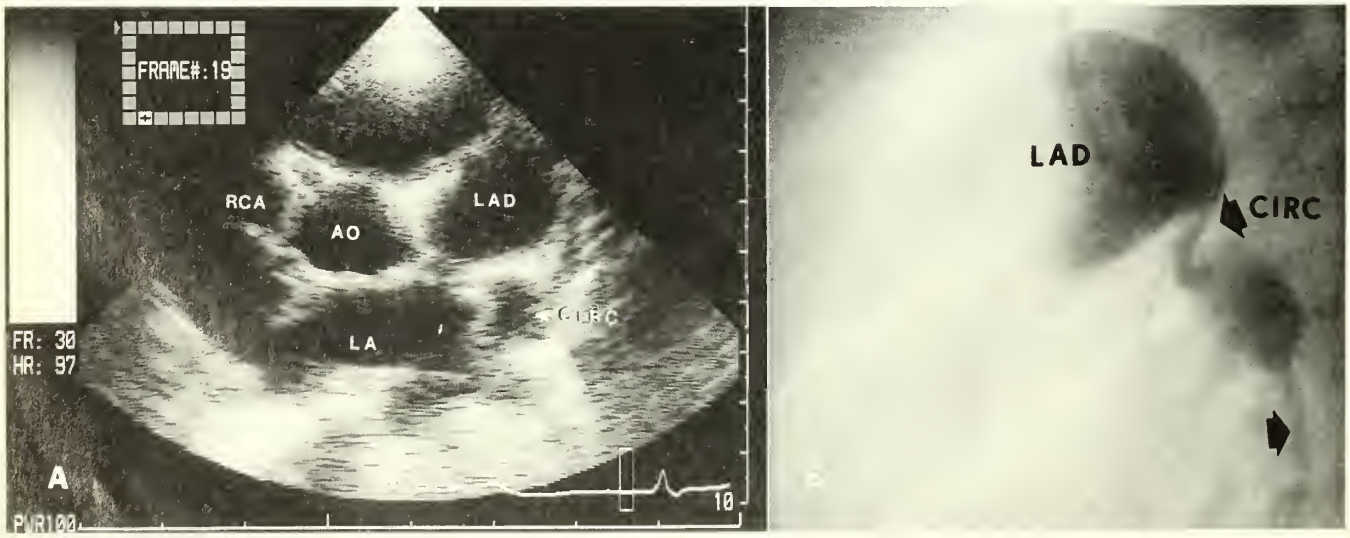

Figure 4.—A, A short-axis echocardiographic image was taken at the level of the aorta (AO) 6 months into illness. The left atrium (LA) is also shown. Giant aneurysms are seen in the left anterior descending (LAD) coronary artery, the circumflex coronary artery (CIRC), and the right coronary artery (RCA). B, A cineangiographic frame of the selective LAD and circumflex coronary arteriogram confirms the LAD and circumflex coronary artery aneurysms shown in A.

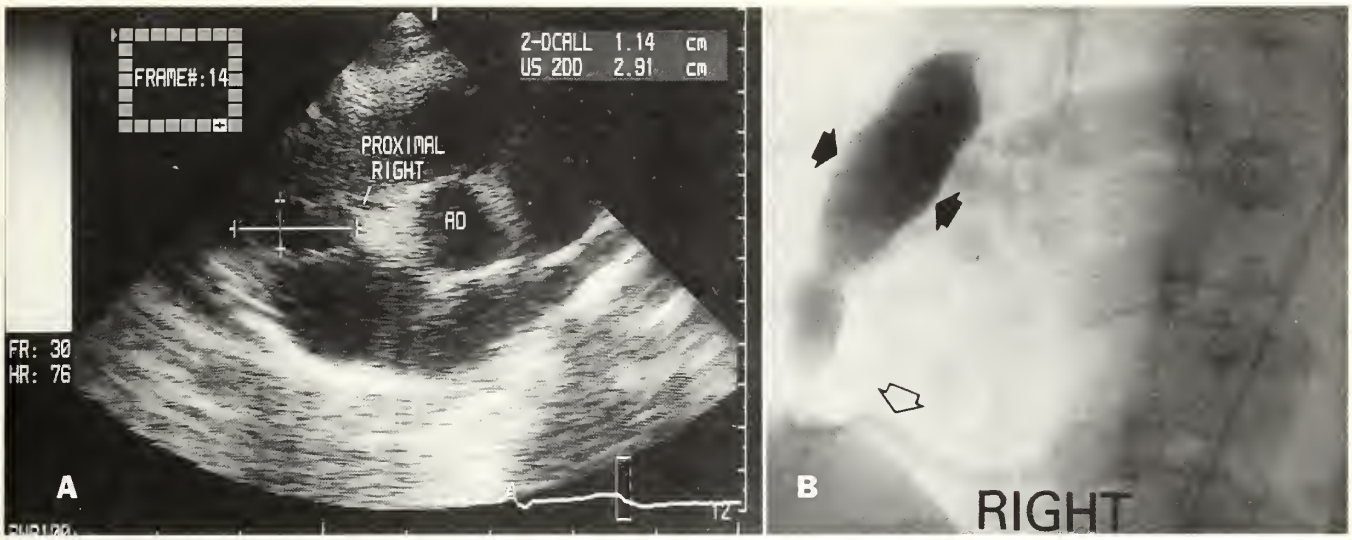

Figure 5.—**A,** A short-axis echocardiographic image taken at the level of the aorta **(AO)** 6 months into the illness demonstrates a fusiform aneurysm of the proximal right coronary artery that is 1.1 cm in diameter and at least 2.9 cm long. **B,** A cineangiographic frame of the selective right coronary arteriogram confirms the presence of the giant fusiform aneurysm shown in **A (closed arrows).** The aneurysm is noted to be nearly 4 times as long as its width. The posterior descending coronary artery is of normal caliber **(open arrow)**.

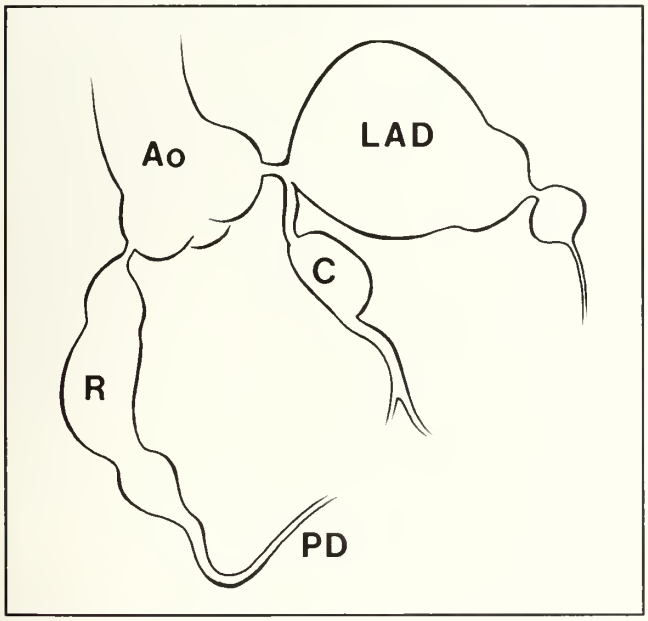

Figure 6.—A diagrammatic representation shows the relative size and location of the aneurysms shown in Figures 3 through 5. Ao = aorta, C = circumflex coronary artery, LAD = left anterior descending, PD = posterior descending coronary artery, R = right coronary artery

confusing signs of systemic inflammation, even in the absence of fever, should have Kawasaki syndrome considered as part of the differential diagnosis.

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Anion and Osmolal Gaps in a Patient With Alcoholism

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PERSONS WITH ALCOHOLISM frequently present with myriad acid-base, fluid, and electrolyte abnormalities identified during evaluation for nonspecific symptoms. The case described in this report highlights the complexity of laboratory derangements seen in a patient with alcoholism with concomitant ketoacidosis and substituted alcohol ingestion.

Report of a Case

The patient, a 58-year-old man, presented to the emergency department with lethargy, tachypnea, and expressive aphasia. Three days before admission, the patient had the development of aphasia without other associated neurologic symptoms. As a result, he became despondent and started a drinking binge of about a fifth of bourbon whiskey per day. Over the ensuing days, the patient consumed only alcohol. On the day of admission, he was found to be lethargic, aphasic, and vomiting. He did not have chest or abdominal pain,

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ABBREVIATIONS USED IN TEXT

NAD = nicotinamide-adenine dinucleotide
NADH = reduced form of NAD

bleeding, fevers, chills, sweats, suicidal ideation, or toxic ingestions. There was no history of liver or renal disease, diabetes mellitus, or injection drug use.

The patient had a history of myocardial infarction with an apical ventricular aneurysm noted on a previous cardiac catheterization. A year before admission, the patient had a reversible ischemic neurologic event manifested by expressive aphasia and right hemiparesis. Echocardiography revealed severely reduced left ventricular function and a left ventricular mural thrombus. Because of the chronic and severe nature of the alcohol abuse, anticoagulation therapy was not begun. The only medication was an enteric-coated aspirin daily.

On physical examination the patient was thin, disheveled, and lethargic but in no acute distress. His temperature was 36.6°C (97.9°F); respiratory rate, 22 per minute; pulse rate, 80 beats per minute; and blood pressure, 130/80 mm of mercury, supine, with a pulse of 100, and 76/40 mm of mercury, upright, with a pulse of 120. Pertinent findings on the examination were the absence of head trauma, full extraocular movements without nystagmus, and the fundi, heart, and abdomen were normal. On neurologic examination, the patient had a normal level of consciousness and orientation. Although his speech was garbled, cranial nerve, motor, and sensory systems were normal.

Admitting laboratory values were as follows: serum sodium, 139 mmol (mEq) per liter; potassium, 4.8 mmol (mEq) per liter; chloride, 102 mmol (mEq) per liter; bicarbonate, 8 mmol (mEq) per liter (normal 22 to 28); urea nitrogen, 5.0 mmol per liter (14 mg per dl); creatinine, 124 μmol per liter (1.4 mg per dl); and glucose, 4.2 mmol per liter (75 mg per dl). Arterial blood gas determinations with the patient breathing room air revealed a Po_2 of 97 mm of mercury, a Pco_2 of 22 mm of mercury (normal 35 to 45), and a pH of 7.12 (normal 7.36 to 7.44). A blood alcohol level was 16 nmol per liter (72 mg per dl), a serum ketone test was negative, and serum osmolality was 315 mmol (mOsm) per kg. A urinalysis showed a specific gravity of 1.017, a pH of 5, large ketone bodies, and no glucose, cells, or crystals. A hematocrit was 0.47. An electrocardiogram and a chest x-ray film were normal.

In the emergency department, the patient was administered intravenous thiamine, dextrose, saline solution, and 44 mEq of sodium bicarbonate; he was then admitted to the intensive care unit. Based on additional information and laboratory studies (see discussion), management led to an improvement in the patient's clinical and metabolic states over the ensuing 24 hours. The patient was lost to follow-up after discharge.

Discussion

This poorly nourished, volume-depleted man with chronic alcoholism presented with a serious and confusing constellation of metabolic derangements, the most obvious being profound acidemia. With the acidosis and a depressed serum bicarbonate level as the primary change, the patient had a metabolic acidosis that was accompanied by a compensatory drop in the Pco_2 level.[1] In a simple (as opposed to complicated) metabolic acidosis, the Pco_2 should fall by 1 to 1½ times the fall in serum bicarbonate level, which was the case at the time of this patient's admission. The anion gap, calculated by subtracting the sum of the serum chloride and bicarbonate levels from the serum sodium level (normal anion gap = 12 ± 4 mmol per liter), is 29, leaving a minimum of 13 mmol per liter of organic anions remaining after buffering of the acid.[2]

The more common causes of an anion gap metabolic acidosis include methanol, uremia, lactate, ethylene glycol, salicylates (or aspirin), and ketone bodies. In this patient, tests for the presence of serum methanol, ethylene glycol, salicylate, and ketones were negative, and the lactate level was 5.9 mmol per liter (normal 0 to 2.5). Therefore, when the lactate value is subtracted from the unexplained anion gap (13 mmol per liter), 7.1 mmol per liter of organic anions remain.

In the initial laboratory data, there was a discrepancy between the serum ketone level, which was normal—that is, no ketone bodies were detected—and the urine ketone level, which was reported as high. This can be explained on the basis that there is a low renal threshold for ketoacid excretion and the serum test for ketones is a nitroprusside reaction that is much more sensitive for acetoacetate than it is for β-hydroxybutyrate or acetone, the other two ketone bodies. The urine dipstick test, however, is a ferrous cyanide reaction that is more sensitive than the nitroprusside test in detecting both acetoacetate and acetone. Neither of the tests detects β-hydroxybutyrate.[3] In ketone metabolism, acetoacetate is converted to β-hydroxybutyrate through an enzymatic reaction using the enzyme β-hydroxybutyrate dehydrogenase. With an excess amount of the reduced form of nicotinamide-adenine dinucleotide (NAD), or NADH, the reaction leads to accumulation of β-hydroxybutyrate, the reduced form that is not measured by standard laboratory procedures. Also, acetoacetate when present in large quantities may be converted through a nonenzymatic reaction to acetone, which can give a positive ferrous cyanide reaction.

During the first 18 hours of his hospital admission, the patient's serum bicarbonate level rose to 21 mmol per liter, accompanied by a rise in the serum pH. During this same period, the urine ketone level remained high while the test for serum ketones, initially negative, became positive in an undiluted form. This apparent worsening of the serum ketone level, while other measurements suggested that the patient's condition was improving, can be explained by the conversion of β-hydroxybutyrate back to acetoacetate, as a predominance of NAD drove the reaction in the opposite direction during treatment. Because acetoacetate is the substance primarily measured in the nitroprusside reaction, the increasingly higher serum ketone levels do not reflect worsening of the metabolic condition but rather the conversion of the ketones to a form that is now measured by the laboratory test.

Another explanation, however, for the ketones detected in the urine would be the presence of large amounts of acetone. The serum plasma acetone level, measured by gas chromatography at the time of admission, was 4,305 μmol per liter (25 mg per dl), which was higher than would be expected from a mere conversion of acetoacetate accumulation. Acetone, as opposed to the ketoacids acetoacetate and β-hydroxybutyrate, is a nonacidic ketone that does not cause a metabolic acidosis. Although the presence of serum acetone may be the product of both the level and duration of the

elevation of acetoacetate, another cause of an elevated acetone level, particularly in chronic alcoholism, is isopropyl alcohol ingestion. This is explained by the fact that isopropyl alcohol is metabolized in the liver directly to acetone, which is subsequently excreted in the lungs, leading to a typical acetone breath, or, in larger quantities, through the urine, producing ketonuria.[4]

Laboratory results six hours after admission revealed an isopropanol level of 1.50 mmol per liter (9 mg per dl). As is often the case, the patient had denied substitute alcohol ingestion despite inquiries by several examiners. Although a variety of compounds contain isopropanol, including glass cleaners, detergents, lacquer thinners, and windshield washer fluid, the most common source of isopropanol implicated in surreptitious ingestions is rubbing alcohol. Isopropyl alcohol, along with ethylene glycol and methanol, are three toxins often ingested by persons with chronic alcoholism as substitute alcohols.[5] All three substances are metabolized initially by the same enzyme, alcohol dehydrogenase. Methanol ingestion results in formic acid accumulation, whereas ethylene glycol causes glycolic acid accumulation. Methanol and ethylene glycol cause a severe metabolic acidosis whereas isopropanol, which increases levels of acetone, the nonacidic ketone body, does not cause acidosis.

In addition to the acidosis as a distinguishing feature, methanol ingestion may cause visual blurring due to a severe papillitis and retinal edema, and ethylene glycol ingestion can cause a delayed and severe acute renal failure due to the accumulation of calcium oxalate and hippurate crystals in the urine. The absence of these findings, however, does not rule out these intoxications in a patient with acidosis. Because ethanol is also metabolized by alcohol dehydrogenase and has a 10 to 100 times affinity for this enzyme compared with the substitute alcohols, the coingestion of ethanol may delay the metabolism and toxicity of these alternative alcohols. In this patient, the presence of ethanol at the time of ingestion may have delayed the metabolism of the isopropyl alcohol. At high serum levels, isopropanol can cause coma and severe hypotension, which may be indications for the institution of hemodialysis. In most instances, though, supportive treatment with intravenous fluids is adequate.[4]

A second metabolic abnormality in this patient was the elevated serum osmolality as measured in the laboratory. The serum osmolality can be calculated by a simple formula of 2 times the serum sodium level plus the glucose level divided by 18 plus the urea nitrogen level divided by $2.8 - 2 \times ([\text{sodium} + \text{glucose}]/[18 + \text{BUN}])/2.8$ (using conventional units). In this instance, a calculated serum osmolality is 287 mmol per kg of water (normal, 280 to 300). The serum osmolality is a measure of either the serum water content or the presence of foreign low-molecular-weight substances.[6] The osmolal gap is the difference between the measured serum osmolality and the calculated osmolality, with a normal gap being 10 mmol per kg of water or less. In this patient, the osmolal gap is 28 mmol per kg of water ($315 - 287$), suggesting the presence of unrecognized low-molecular-weight substances. The low-molecular-weight substances that can cause increases in serum osmolality (and, in parentheses, the contribution per milligram per deciliter of each substance) are as follows: methanol (0.34), ethanol (0.22), ethylene glycol (0.20), acetone (0.18), and isopropanol (0.17).[5] In this patient, measurable ethanol, acetone, and isopropanol levels contribute to the measured serum osmolality. Using the conversion factors and the measured levels, the calculated serum osmolality would be 287 + ethanol level (72×0.22) + acetone (25×0.18) + isopropanol $(9 \times 0.17) = 309$. Therefore, using the recalculated serum osmolality, the serum osmolal gap is 6 mmol per kg of water ($315 - 309$), within the normal range. When ethanol levels are considered, ethanol is the commonest cause of an elevated osmolal gap.

Despite ethanol and isopropanol ingestions, the cause of the profound metabolic acidosis in this patient remains unexplained. The slight increase in the serum lactate level could be explained by a combination of alcohol and intravascular volume depletion—the patient had pronounced orthostatic blood pressure changes on physical examination—leading to inadequate tissue perfusion and lactate production. As noted earlier, however, the lactate level alone does not account for the entirety of the anion gap. Although the serum acetone could account for the positive ferrous cyanide reaction in the urine, the acetone level cannot explain the acidosis, as acetone is a nonacidic ketone body.

The initial serum glucose level was normal—indeed, the capillary blood glucose level measured immediately on arrival was low, 2.2 mmol per liter (40 mg per dl), excluding diabetic ketoacidosis as a cause of the anion gap metabolic acidosis. Therefore, the remaining explanation for the acidosis is that this patient had alcoholic ketoacidosis, a disorder first described in 1940. Typically patients with alcoholic ketoacidosis have chronic alcoholism and have been drinking heavily, are poorly nourished, and begin vomiting.[7] Patients often have tachycardia and volume depletion and have abdominal tenderness on physical examination. In one series, a third of patients had associated alcoholic pancreatitis.[8] It is not clear why alcoholic ketoacidosis develops in only a small group, as poor nutrition, nausea, and vomiting are commonly seen in alcoholic patients presenting to emergency departments. In those persons in whom alcoholic ketoacidosis does develop, however, it appears that they are more likely to have recurrent episodes. Of note is that 18 months before this admission, the patient had been seen in the emergency department, at which time an anion gap of 27 was recorded. At that time, the patient left before an evaluation could be completed.

Although the inciting factors for alcoholic ketoacidosis are not completely understood, the primary pathophysiology of the disorder appears to be due to low circulating insulin levels.[8] Three derangements contribute to the hypoinsulinemia. First, starvation causes decreased glycogen stores, which inhibits insulin production. Starvation also causes an increase in free fatty acid production in the liver, which serves as fuel replacing glucose in the brain, kidneys, and other major organs. Second, the metabolism of ethanol to acetaldehyde and acetate leads to an increase in the ratio of NADH to NAD, which inhibits gluconeogenesis and, subsequently, depresses insulin production and release. Because the ketoacids are by-products of fatty acid metabolism, the ketoacids (acetoacetate and β-hydroxybutyrate) accumulate when the ketoacid production exceeds the ability of the body to clear the substances. The increased NADH:NAD ratio resulting from ethanol metabolism actuates the enzymatic reaction from acetoacetate to β-hydroxybutyrate, explaining the severe acidosis seen with a negative serum nitroprusside reaction. Third, extracellular and intravascular volume depletion cause elevations in serum catecholamine, cortisol,

and growth hormone levels that suppress insulin production and increase glucagon release, both of which stimulate free fatty acid production and the development of ketoacids.

This patient had not eaten for at least two days, had been drinking heavily, and was volume depleted on initial examination. This is an ideal milieu for the development of alcoholic ketoacidosis. A recent review of 74 patients with alcoholic ketoacidosis showed that, in addition to the typical historical and physical features noted in this patient, two thirds had detectable blood alcohol levels at the time of admission, the mean serum bicarbonate level was 13 mmol per liter, and 56 patients (about 75%)—in contrast to this patient—had complicated acid-base disturbances.[8]

The treatment of alcoholic ketoacidosis relies solely on replenishing the intravascular volume and administering dextrose-containing solutions. Both volume and dextrose replenishment will increase insulin release, thereby turning off free fatty acid and ketoacid production and resulting in an increased NAD:NADH ratio. The latter metabolic event stimulates the enzymatic reaction from β-hydroxybutyrate to acetoacetate, explaining the rising ketoacid measurements by the serum nitroprusside test during treatment. Insulin administration is not necessary, as rising serum insulin levels will result solely from administering the fluids and dextrose. Administering thiamine, before initiating treatment, however, is critical because a person with the malnutrition of chronic alcoholism may have low thiamine reserves. Because thiamine is a cofactor in carbohydrate metabolism, administering large concentrations of dextrose to a patient with marginal thiamine stores may result in the remaining thiamine being consumed, which would precipitate acute Wernicke's encephalopathy.[9] Hypomagnesemia, seen often in these patients, may contribute to the development of encephalopathy. Also, because severe hypophosphatemia and hypokalemia are common accompaniments of the treatment of alcoholic ketoacidosis,[8] initially low levels of phosphate and potassium should be corrected before administering dextrose.

Another possible contribution to this patient's elevated osmolal gap could be alcoholic ketoacidosis itself. A recent study examined the osmolal gap in patients with lactic acidosis and alcoholic ketoacidosis after correcting for the contribution of ethanol.[10] Half of the patients with alcoholic ketoacidosis still had an elevated osmolal gap after the correction for ethanol and the exclusion of the other low-molecular-weight toxins mentioned earlier. The specific cause of the increased osmolal gap in alcoholic ketoacidosis has not been clarified, but this finding suggests that an increased osmolal gap, corrected for ethanol, may not be specific for substituted alcohol ingestion. This issue becomes more important when, as in this patient, an alcoholic patient presents with profound acidosis and an elevated osmolal gap and methanol and ethylene glycol levels are not immediately available from the laboratory. Whereas the therapy for methanol and ethylene glycol ingestion would be the intravenous administration of ethanol to block metabolism—and hemodialysis in patients who have ingested ethylene glycol—the treatment of alcoholic ketoacidosis would not involve either of these therapies. The authors suggest that, if the serum osmolal gap is greater than 25 after correcting for ethanol and serum levels of methanol and ethylene glycol are not immediately available, the patient should be treated with intravenous ethanol.[10]

The final issue in the management of this patient is the use of sodium bicarbonate to treat metabolic acidosis. An argument against the use of supplemental bicarbonate is that such therapy induces hypercapnia, thereby aggravating intracellular acidosis. Also, paradoxic cerebrospinal fluid acidosis may result, ionized calcium levels are depressed, and there is no improvement in outcome in those patients treated with sodium bicarbonate. Arguments for treating severe acidosis with bicarbonate, however, include the fact that such therapy "buys time" while the underlying cause of the acidosis, such as sepsis, is determined and treated (an analogy being treating a fever with antipyretics while looking for the source).[11] This concept may be particularly important for patients with serum bicarbonate levels less than 10 mmol per liter, as further small degrees of blood acidification greatly decrease the pH. Also, the acidemia has a negative ionotropic effect that, when combined with peripheral venoconstriction and an increase in central blood volume, may precipitate congestive heart failure. Recent controlled studies evaluating the use of bicarbonate supplementation in patients with lactic acidosis and diabetic ketoacidosis have failed to show a clear benefit.[12,13] In the recent series of patients with alcoholic ketoacidosis, some of whom had pH levels as low as 7.0, all responded well to treatment with fluid and dextrose replenishment alone without supplemental sodium bicarbonate.[8] Although this issue remains without consensus, many clinicians advocate for sodium bicarbonate supplementation in patients with metabolic acidosis associated with a pH of less than 7.1.

In summary, this patient with chronic alcoholism with severe metabolic acidosis and an elevated osmolal gap had both alcoholic ketoacidosis and isopropanol ingestion. Recognition of the myriad acid-base and electrolyte disturbances associated with chronic alcohol ingestion and a stepwise assessment of initial laboratory measurements are crucial to developing an appropriate management plan for substitute alcohol ingestion and ketoacidosis.

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Editorials

Why Does the Blood Not Coagulate?

A British physician, T. W. Jones, asked 150 years ago, "Why does the blood circulating in the vessels not coagulate?"[1] We still seek an answer to this logical question. Even children know that when they cut themselves the blood that oozes from the wound quickly clots. Why does it wait to do this until it has left the injured blood vessel? Innumerable theories have been offered in explanation.[2]

A host of experimental work, some of it recounted skillfully elsewhere in this issue by Samuel Rapaport, MD,[3] teaches us the steps that lead to coagulation when blood is withdrawn from the body into the artificial world of test tubes. As Lister appreciated more than a century ago,[4] one way that the clotting process may begin is that shed blood touches a "foreign" surface, that is, a surface other than the normal endothelial lining of the vascular tree. The initiation of clotting in this manner is described as the intrinsic pathway of thrombin formation. Alternatively, as described long ago by Thackrah,[5] clotting also comes about when blood comes into contact with injured tissues. In modern terms, a clot-promoting agent furnished by injured tissues, variously called tissue factor or tissue thromboplastin, forms a complex with a plasma protein, factor VII, that then initiates thrombin formation through reactions of the extrinsic pathway of clotting. The terminology is confusing, as in each case something extrinsic to the blood is responsible for starting the clotting process.

A friend of mine was fond of saying, "It is we who are simple, not nature." Dividing the steps leading to thrombin formation into intrinsic and extrinsic pathways makes it easier to draw diagrams, but biology is seldom that accommodating. When Rapaport and co-workers showed that the prothrombin time was shortened on exposing plasma to glass,[6] it was evident that the separation of the two pathways was mostly in the mind of the observer. When plasma comes into contact with glass, this foreign surface activates Hageman factor (factor XII), and activated Hageman factor, it turned out, can change factor VII to its enzymatically active state.[7,8] In the years since these observations were published, seemingly innumerable examples of cross-reactions between the intrinsic and extrinsic pathways have been found, some described in Rapaport's review.

If this tells us how blood can coagulate, it does little to answer Jones's question. The logic of biology suggests that the potent reactions leading to the formation of a clot cannot go unchecked; the alternative would be unbridled intravascular clotting. Some early experimental observations offering an explanation for modulation of the clotting process were described by Morawitz and Rettger, who found that plasma itself could inactivate thrombin, protecting circulating blood from the inadvertent formation of this enzyme.[9,10] This agent, antithrombin III (or just "antithrombin"), is of peculiar clinical interest. For the most part, the anticoagulant action of heparin depends on its ability to form a complex with antithrombin III. Antithrombin III bound to heparin inactivates not only thrombin but also factor Xa (activated Stuart factor), factor IXa (activated Christmas factor), factor XIa (activated plasma thromboplastin antecedent), and factor XIIa (activated Hageman factor). Heparin and the heparan proteoglycan of blood vessel walls also combine with another plasma protein, heparin cofactor II, to form a second inhibitor of thrombin, a further check against the formation of fibrin.

Other plasma proteins provide still other controls over the steps of the intrinsic pathway of thrombin formation. $C\bar{1}$ inhibitor blocks the enzymatic activity not only of the first component of complement but also of factor XIIa, factor XIa, and plasmin. α_1-Antitrypsin inhibits factor XIa. And protein C, a protease that is activated by thrombin and abetted by a nonenzymatic cofactor, protein S, inactivates the thrombin-altered forms of both factor VIII (antihemophilic factor) and factor V (proaccelerin).

A different class of inhibitors of clotting has had some recent attention. Suspensions of platelets or of nucleated peripheral blood cells and the supernates of such suspensions inhibit the activation of Hageman factor.[11,12] The agent or agents responsible have not yet been identified but seem different from other described inhibitors of clotting. Even more exciting, the supernates of cultured human and bovine vascular endothelial cells and the cytoplasmic fluid of human vascular endothelial cells inhibit the activation of Hageman factor.[13,14] These inhibitors make "sense" teleologically, for they protect the intrinsic pathway of thrombin formation from inadvertent activation by these biologically active cells. That this hypothesis may have merit comes from an examination of the odd fact that filariae or schistosomes residing in human blood vessels do not seem to stimulate the growth of thrombi. In both cases, the offending organisms appear to be covered on their surfaces with inhibitors of the activation of Hageman factor.[15,16]

In his review, Rapaport summarizes what is now known about yet another controller of clotting, tissue factor pathway inhibitor (née extrinsic pathway inhibitor or lipoprotein-associated inhibitor). This protein has a curious history, some of it reviewed by Broze and Miletich and by Sandset and Abildgaard.[17,18] In 1919 Obata, trying to understand the pathogenesis of eclampsia, injected saline extracts of human placenta into mice.[19] These animals had convulsions, became comatose, and died within minutes. These experiments seemed a replay of those of de Blainville and Wooldridge, whose similar studies laid the groundwork for our current understanding of disseminated intravascular coagulation.[20,21] But Obata carried his studies further. When the placental extract was incubated with serum before it was injected, it appeared to lose its toxicity. Confirming these experiments, Schneider found that the agent in serum that inhibited the toxicity of placental extracts was heat-labile.[22,23] At the same time, Thomas reported that the intravenous injection of brain or lung tissue into mice induced ataxia and convulsions, observations reminiscent of those of Obata.[24,25] Thomas, too, found that mammalian serum inhibited the toxic effect of these tissue extracts. The effect of serum was dependent on the presence of calcium ions and was abolished by heating the serum at 65°C for 30 minutes. Thomas also noted that the inhibitory property of serum could be adsorbed to the tissue particles. Thus, by 1947 it was clear that serum contained an inhibitory activity that would neutralize what is now called tissue factor or tissue thromboplastin, an interpretation not lost to these early investigators.

Several groups of investigators have extended these ear-

lier studies.[17,26,27] In his review, Rapaport clearly summarizes what is known about tissue factor pathway inhibitor. This inhibitor successively binds factors Xa and VIIa, effectively reducing the generation of thrombin. What makes these observations particularly exciting is evidence that, in animals, depletion of this inhibitor may enhance disseminated intravascular coagulation. Rapaport's speculations about this inhibitor's role in the control of disseminated intravascular coagulation find support in experiments of Day and colleagues.[28] These investigators showed that administering recombinant tissue factor pathway inhibitor suppressed the induction of disseminated intravascular coagulation in rabbits infused with tissue thromboplastin, bringing a modern explanation to the observations of Obata and those who followed. It is not hard to speculate that recombinant tissue factor pathway inhibitor may find therapeutic use in patients with disseminated intravascular coagulation.

All this would be esoteric were it not for the fact that hereditary deficiencies of one or another of the inhibitors of clotting may be complicated by serious pathologic changes. Thus, deficiencies of antithrombin III, heparin cofactor II, or proteins C or S are accompanied by a tendency to recurrent thrombosis.[29] But patients with one or another of these deficiencies provide a puzzle not yet clearly addressed. For example, hereditary partial deficiency of antithrombin III is lifelong. From time to time, perhaps at intervals of many years, patients who have this heterozygous deficiency of antithrombin III may sustain thrombosis. I assume that the initiation of thrombosis takes but a short time. Why is it these patients do not have continual, major intravascular clotting? Another enigma surrounds the deficiency of $C\bar{1}$ inhibitor, a protein that inhibits both clotting and fibrinolysis. A deficiency of $C\bar{1}$ inhibitor is not accompanied by a thrombotic tendency, but rather is the pathogenetic feature of hereditary angioneurotic edema.[30] Sometimes nature tells us what are important biologic reactions, regardless of what we think we know from laboratory studies.

Another puzzle close to my heart is the persistence of Hageman factor throughout the mammalian kingdom, even though its absence does not seem to impair life. This seems to violate the principle that useless systems are cast off during the course of evolution. If this principle has merit, what secret need is there for Hageman factor, and, if this is true, why is the absence of Hageman factor not a handicap?

And then there is the unsettling intertwining of the reactions of clotting, fibrinolysis, complement, and inflammation. Some years ago, when I tried to write a synthesis of what I knew about blood clotting, I found that, try as I would, I could not separate what I knew about coagulation from what I thought I knew about these other systems.[31] Trained to look at each of these systems as a discrete entity, I found it difficult to accept that in real life the reactions of these four systems are hopelessly entangled. Like all great revelations, it did not take long to find that my views were not the news of the week; yet my unitarian synthesis offended a scientific bureaucracy I did not even know existed.

A good review should stimulate readers to think not just about problems solved but about questions not yet answered. Rapaport's review fits this bill.

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The Final Career

"RETIREMENT" has many definitions. The third offering in the *American Heritage Dictionary* says, "To withdraw from business or public life so as to live at leisure on one's income, savings or pension." It reverberates with doom—a doleful prescription for an early demise.

Because the editors were kind enough to ask me to comment on the subject, presented so tidily and provocatively by Virshup and Coombs[1]—I am a novice retiree . . . a mere 13

months—I feel obliged to share with you my personal definition. It goes something like this. Retirement is the final career for you *and* your spouse, if you have one, since no one retires alone if one is married. When your last graduate student has been dropped from the family payroll; when you no longer leap out of bed at the crack of dawn with a song in your heart in eager anticipation of beating the freeway gridlock or making early morning rounds before spending another day in the office; when your wise and wily financial adviser smilingly gives you the green light: Yes, notwithstanding unforeseen fluctuations in the market, you have enough squirreled away to live for the next 20 or 30 years almost in the manner to which you have become accustomed; and—perhaps most important—you and your spouse really believe that you will have fun living eyeball-to-eyeball 24 hours a day, seven days a week, forevermore. If all the responses are positive, you are ready to retire—*if you have a plan.* This is your final career. And, make no mistake, it is a career, and it will require every bit as much planning (perhaps more) than any other of your careers.

I may be a novice retiree, but I am a veteran observer of unsuccessful retirements. One was of a tough, vigorous 62-year-old four-star general who commanded a corps in combat and an army in peacetime. He could not wait to "hang it up and devote my life to golf, hunting, fishing, and reading all the books I never had time for." You know the story. After six months he was bored out of his gourd; at 12 months he was severely depressed. Within two years he was dead. You can change the characters and the scenery, but the story is all too familiar.

Virshup and Coombs present a much more optimistic outlook: "Most physicians enjoy the freedom and activities of retirement . . . . Fears of boredom and deterioration are unfounded." This has been my experience as well, but there are a few fascinating facts that emerge from their study. Only 27 responded that they had prepared "extremely well" for retirement; 52 said "fairly well," 13 "so-so," and 8 poorly. To me, this means that 73 were asking for trouble. The authors do not define "prepared," and that to me is the key. Let me explain.

As I alluded to earlier, somewhat facetiously, there are several prime ingredients to a "successful" retirement. Good health is cardinal, and it is a bit more than the blessing of good genes and good luck. At least 30 or 40 years of conscious attention to the controllables, such as rational dietary discipline, reasonable regular exercise, avoidance of cigarettes and excess alcohol, insightful management of stressors, and buckling up the seat belts, pay off. It is a tragedy to arrive at retirement in a state of physical disrepair—especially if it could have been prevented—and find your options severely limited.

Next comes financial security. One would assume that this should not be a problem for physicians, but all too often even my wisest colleagues underestimate what will be required to maintain their standard of living. Early planning with a "wise and wily" financial adviser is mandatory.

The next facet of planning comes with a realistic calculation of how to balance intellectual, physical, cultural, and social activities. (This is where my unfortunate general ran aground). For each person, this balance will be intimately personal, and this is where many hours of long, serious conversation with your spouse are critical—again, many years in advance of that great day.

Despite how much a person loves being a physician (or a mathematician or a carpenter), there will come a time to step aside. I am always saddened by the vision of emptiness I perceive when a friend says, "I love my work so much that I plan to die in harness." How narrow and impoverished is a life that has not tasted some of the wonderful things that lie beyond any "work" and has not been tempted to savor them a little more. Admittedly, sometimes the best-laid plans do not ensure success in retirement. Ill health is always an evil joker in the deck. So is a sudden unplanned financial setback ("Janice just called from Swarthmore; she has changed her mind and now wants to go to medical school. And Ted has finally decided to open a men's clothing store!") or *triste dictu*—one morning your spouse of 30 years looks you in the eye and says, "I think we need to give each other a little more space, now that you're home all the time." But the ultimate catastrophe is to wake up each morning and lie awake contemplating the day without joy. Then you must beware the treacherous handmaiden, melancholia.

As in any sound experiment, the only way one can hope to eliminate the uncontrolled variables is to devise a thoughtful protocol—your balanced retirement plan. Each of us must derive the all-important balance that suits a "retirement team." My wife and I retired to a mountaintop in northern New Mexico. We sought serenity, physical beauty, and solitude—after what seemed a lifetime in Megalopolis. The rugged environment demands a great deal of physical activity—cutting and hand-splitting firewood, shoveling and plowing snow in winter, snowshoeing and cross-country skiing, and many other outdoor activities. Our intellectual activities are related to some professional consulting and committee work (not enough to intrude) and pro bono work (it is amazing how desirable you become to national organizations when they know you have the time—but one can pick and choose).

I think we have achieved reasonable balance in our new career. So Virshup and Coombs are right: you will enjoy having the time to sniff the flowers—if you plan ahead.

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Endovascular Neurosurgery—The Marriage of Imaging and Intravascular Therapy in the Decade of the Brain

Disease is from of old and nothing about it has changed. It is we who change as we learn to recognize what was formerly imperceptible.

JEAN-MARTIN CHARCOT
Lectures on the Localization of Cerebral and Spinal Diseases, 1883

INTERVENTIONAL NEURORADIOLOGY, or endovascular neurosurgery, is emerging as a new and recognized subspecialty that bridges the fields of neuroradiology, neurosurgery, vascular surgery, otolaryngology, and neurology. In the late 1970s and early 1980s, this field was sparsely populated by a handful of unconventional physicians in neuroradiology who undertook unconventional treatment of neurovascular disorders that were thought to be untreatable. These included vascular disorders with nearly 100% mortality, such as vein of Galen malformations in the newborn, unresectable large

arteriovenous malformations, and giant intracavernous aneurysms that were not surgically accessible.

These unconventional treatment modalities delivered such materials as silicone spheres, lyophilized human dura, tiny sponges, detachable balloons, and "crazy glue" [cyanoacrylate] to close vessels through intravascular catheters for an increasing spectrum of vascular diseases. The early development of this field was limited by primitive imaging devices, a lack of industry commitment to developing delivery systems to the brain from an endovascular approach (small microcatheters and guide wires), and a lack of adequate resources and funding for evaluating embolic materials implanted in the brain's blood vessels.

The early pioneers in interventional neuroradiology had maverick qualities, however, "to go where no one has gone before" (despite potential malpractice) and to "use what no one has dared to use" in approaches to neurologic diseases. As a result, this field is just now being recognized as one of the emerging specialties of minimally invasive surgery. This is an extremely timely and appropriate evolution for this specialty in the "decade of the brain."

New Technology

Elsewhere in this issue, Barnwell gives an excellent overview of how far this field has evolved in a relatively short period of time.[1] Several factors have contributed to the progress of the past decade:

- Enormous strides have been made in medical imaging by the commitment of major industrial firms to medical technology, including such household names as General Electric, Phillips Corporation, and Toshiba. The development of computed tomography, intravascular ultrasonography, magnetic resonance imaging, and high-resolution digital subtraction angiography, fostered by the medical divisions of these companies, has made the noninvasive and minimally invasive testing and diagnosis of complex medical disorders fairly routine and efficacious.
- Advances in medical technology in microcatheters, steerable guide wires, angioplasty devices, stents, and embolic materials by companies such as Boston Scientific, Cook, Cordis, Target Therapeutics, Pfizer, and Johnson & Johnson have now made it technically feasible to achieve safe and accurate access to almost all territories of the body, including the brain.

Nowhere has this combination of medical imaging and technology had greater influence in diagnosis and therapy than in the brain. In the past we had to rely on inference from clinical testing, indirect testing by electroencephalography, obtrusive observations by pneumoencephalography, and cerebral arteriography by direct carotid puncture. The presence of brain tumors or intracerebral hemorrhages could not actually be visualized but had to be inferred from associated compression of nearby blood vessels and ventricles.

Now we can simply request magnetic resonance imaging or a computed tomographic scan of the brain to rule out structural pathology for the complaints of headaches, seizures, head trauma, or strange and aberrant behavior. Possibly in the near future these procedures will be used for routine screening for strokes—currently the third leading cause of death in the United States. We are only now beginning to realize the important effects this is having on current medical diagnosis and therapy.

Intracranial Aneurysm Therapy

It is estimated from autopsy studies that 1.5% to 8.0% of the population harbors at least one intracranial aneurysm, and 20% of these people have more than one.[2,3] If we assume a 2% incidence for an aneurysm, there are currently 4.8 million potentially treatable patients in the United States. Currently 60,000 to 80,000 cases of acute subarachnoid hemorrhage occur per year in North America, most of which are caused by an intracranial aneurysm. A ruptured intracranial aneurysm causes death in 50% of patients within the first 24 to 48 hours. In a third of those who survive this period of time vasospasm develops, often leading to subsequent stroke or death. The remaining survivors who come to surgery will be normal or near normal in only 50% of cases because of the residual effect of the initial hemorrhage.[4,5]

What if we had the ability to screen patients older than 40 to 50 years for an intracranial aneurysm using magnetic resonance imaging? They could then be treated to prevent the risk of a catastrophic hemorrhage.[6,7] The implications are enormous. We must consider the quality-of-life issue versus the financial effects. First of all, the costs to treat patients under general anesthesia with craniotomy, surgical clipping, and a recovery time of six to eight weeks before returning to work are considerable. Interventional neuroradiologic therapy for such patients is much simpler. After the diagnosis is made by noninvasive testing, patients are admitted to the hospital on the day of the interventional procedure. An arteriogram is done under local anesthesia to confirm where the aneurysm is located. A microcatheter is then guided through the diagnostic catheter and placed directly into the aneurysm under fluoroscopic guidance. An embolic agent is then carefully introduced into the aneurysm to occlude it, usually taking 30 minutes to 2 hours. After observation overnight in the hospital, the patient goes home the next day and can return to work in three to five days after the procedure.[8-10] This results in a savings of about a fifth of the medical cost and a tenth of the time lost from work. The savings in costs and productive work time alone should justify this type of continued research for the safety and efficacy of intracranial aneurysm therapy.

Surgical clipping of aneurysms is now the standard of practice in this country. Endovascular therapy is, however, the standard of practice in Russia at the Kiev Neurosurgical Institute, where all patients with an intracranial aneurysm are first treated by detachable balloons. Only if that treatment fails do patients undergo neurosurgical clipping.[11,12] Similar approaches to therapy are now being advocated by some French neuroradiologic specialists.[13]

Will this type of minimally invasive therapy become the standard of treatment for the rest of the medical community? Only time and further innovations in this technology can tell. Current national and international cooperative studies are evaluating endovascular therapy for intracranial aneurysms using the electrolytic detachable microcoil in surgically difficult aneurysms.[14] If these results are favorable, the next logical step will be to evaluate this treatment for certain types of aneurysms as an adjunct or in place of standard surgical treatment.

Cerebral Angioplasty

The safety and efficacy of cerebral percutaneous transluminal angioplasty for atherosclerotic disease are also being

examined. Angioplasty has been performed in selected cases since the early 1980s in the carotid, vertebral, and intracranial circulation to alleviate cerebral ischemia and stroke.[15,16]

Currently 60,000 to 100,000 patients annually undergo carotid endarterectomy for cerebral atherosclerosis in North America. This therapy has now been validated as efficacious in relieving the risk of stroke in patients with symptomatic stenosis of greater than 70%. The ability of interventional neuroradiologists to treat this disease by balloon angioplasty techniques, similar to those used by cardiologists and vascular radiologists who treat the coronary, renal, iliac, and other peripheral vessels of the body is now being examined.[17] A group approved by the Society of Cardiovascular and Interventional Radiology and the Joint Section on Cerebrovascular Surgery has established a national registry at 15 medical centers in the United States to evaluate this potentially large group of patients.

Head Trauma

The precedent of interventional therapy for treating complex cerebrovascular diseases has already been established in the area of head trauma. Before 1980, the surgical therapy for traumatic carotid-cavernous sinus fistulas was a craniotomy and occlusion of the cavernous sinus or ligation of the extracranial and intracranial internal carotid artery. The surgical complication rate was greater than 30%, and often cure of the fistula was not achieved.

Since 1980 the cure rate by interventional neuroradiology has approached 100%, and the complication rate is less than 4%. It is now becoming the standard of practice that patients with a traumatic fistula involving the carotid or vertebral artery are best managed by interventional techniques; only if these techniques fail should a surgical procedure be considered.[18]

Advantages of Endovascular Surgery

Endovascular therapy has many advantages in the treatment of a wide variety of complex cerebrovascular disorders, including arteriovenous malformations, intracranial aneurysms, traumatic vascular diseases, vasospasm, embolic stroke, and highly vascular tumors. Because the procedures are performed under local anesthesia, the awake patients can undergo constant neurologic monitoring of their clinical condition. As a major brain artery is treated, testing can be done initially to ensure tolerance to therapy. In patients undergoing craniotomy under general anesthesia, this is usually not possible. In addition, blood loss by interventional therapy is minimal; therefore, blood transfusions are unnecessary, even when treating highly vascular malformations or tumors. The stay in a hospital is kept to a minimum, with most patients leaving within 24 to 48 hours following the procedure, with minimal time lost from work.[19,20]

Conclusion

Minimally invasive surgery has had a major effect on many conditions, including endoscopy and lithotripsy for gallstones and kidney stones, angioplasty and stenting for coronary artery and visceral atherosclerosis, and transjugular intrahepatic portosystemic shunts for end-stage liver disease associated with variceal hemorrhage. Industry will continue to fund the research and development of this area as the next generation of imaging and medical devices is produced. In the future it is possible that endovascular surgery will be performed using real-time magnetic resonance imaging and intravascular ultrasonography without the need for radiographic fluoroscopy.

Government needs to recognize that it should not overly restrict the medical device industry by rules, regulations, and bureaucratic processes. The federal government may facilitate advances in device development by establishing another mechanism through the regulatory process to decrease the enormous costs and liability associated with new and innovative technology.

The implications for improvement in the quality of life for persons with cerebrovascular disease are enormous. Health care costs should also be substantially reduced by interventional techniques if comparable or improved morbidity statistics can continue to be achieved.

Future breakthroughs in minimally invasive therapy will rapidly change the way medicine is currently being practiced as these techniques continue to evolve for all parts of the body including the brain.

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Correspondence

The Editors will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words and must be typewritten, double-spaced, and submitted in duplicate (the original typescript and one copy). Authors will be given the opportunity to review the editing of their correspondence before publication.

Late Relapse of Tick-borne Relapsing Fever Following Treatment With Doxycycline

To THE EDITOR: Tick-borne relapsing fever is contracted during the summer and fall in scattered rural locales throughout the western United States. Most infections are due to *Borrelia hermsii*, which is transmitted by a soft tick, *Ornithodoros hermsii*, that feeds on rodents and commonly infests rodent nests in burrows and abandoned shelters.[1-3] Because *Ornithodoros* ticks usually feed nocturnally for brief 5- to 20-minute periods, actual tick bites are rarely remembered by affected patients.[1] Illness occurs 4 to 18 days following inoculation and is characterized by the sudden onset of fever associated with severe myalgias, arthralgias, and malaise. Untreated patients may suffer repeated relapses of fever and symptoms for weeks to months before the illness resolves. Relapses correlate with changes in the antigenic expression of a specific *Borrelia* coat protein, which enables the spirochete to escape specific host antibody and multiply in the blood.[4,5] When spirochetes cannot be detected in the blood, borreliae may reside in organs such as the spleen, liver, kidneys, and brain, which serve as reservoir sites for future blood-borne relapses of disease.[1,5] Because of its ability to rapidly eliminate blood-borne borreliae, tetracycline (or doxycycline) is considered the drug of choice for treating tick-borne relapsing fever.[6] Therapy for five to ten days is believed sufficient to achieve complete eradication of borreliae and prevent subsequent relapse.[7] We describe the case of a patient who had a documented recurrence of tick-borne relapsing fever five months after treatment with doxycycline.

Report of a Case

In July 1990, a previously healthy 71-year-old male university geology professor was admitted to the University of Washington (Seattle) Medical Center because for three days he had had fever, chills, myalgias, malaise, weakness, and anorexia. While on a geology field trip seven days before admission to hospital, he had slept overnight in a decrepit, abandoned ranch house in a rural area of eastern Washington (Lincoln County). On admission, he was febrile with a temperature of 38°C. Orthostatic hypotension was present. Laboratory studies revealed a hematocrit of 0.42, a leukocyte count of 5.7×10^9 per liter, a platelet count of 67×10^9 per liter, and an erythrocyte sedimentation rate of 78 mm per hour. A blood smear revealed numerous extracellular spirochetes, consistent in morphology with *Borrelia* species. Based on the diagnosis of relapsing fever, a regimen of intravenous doxycycline, 100 mg every 12 hours, was started. After three days of therapy, a follow-up blood smear revealed no spirochetes, and the patient was discharged on oral doxycycline therapy, 100 mg twice a day, to complete a ten-day course of antimicrobial therapy. At a follow-up visit a month later, the patient felt well; laboratory studies revealed a hematocrit of 0.38, a leukocyte count of 4.2×10^9 per liter, and a platelet count of 449×10^9 per liter. The patient said he had complied with the regimen of doxycycline therapy following hospital discharge and remained asymptomatic until December 1990, when fevers, rigors, anorexia, malaise, and myalgias recurred. A blood smear again showed spirochetes consistent with *Borrelia* species, although fewer in number than on the previous smear five months earlier. His symptoms resolved within 24 hours of treatment with oral doxycycline, 100 mg every 12 hours, which was continued to complete a 14-day course of therapy. No subsequent relapses have occurred. He has had no activities in rural areas since his hospital discharge.

Discussion

To our knowledge, this report represents the first documented case of unequivocal relapse of tick-borne borreliosis following currently recommended tetracycline therapy. A previous report suggested relapse of disease in a child after a ten-day course of tetracycline but failed to show recurrence of blood-borne spirochetes.[8] Our review of reports of tick-borne relapsing fever in the English-language literature did not identify another case of relapse following tetracycline therapy.

This report serves to remind physicians that tick-borne relapsing fever remains locally endemic in the western United States. Our experience indicates that currently recommended therapy may not be sufficient to achieve cure in all cases of tick-borne relapsing fever. We suggest that consideration be given to a more prolonged course of tetracycline (or doxycycline) therapy to prevent disease recurrence in severe cases of tick-borne relapsing fever.

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Judaism and the Belief in an Afterlife

To THE EDITOR: In her article, "The Effect of Values and Culture on Life-Support Decisions," Jill Klessig, MD, emphasizes the importance of health professionals understanding diverse beliefs around life-and-death issues. She goes so far as to say that "It is unacceptable for a health professional to be ignorant or insensitive to the cultural beliefs of a dying patient."[1] She concludes her discussion on Orthodox and non-Orthodox Jews by categorically asserting that ". . . Jews do not have the same belief in an afterlife or reincarnation that other faiths do."

This is not so. Judaism has always maintained a belief in an afterlife.[2] Passages in the Hebrew Bible range from implications on the fate of the individual after death (2 Kings 2:11; Samuel 28:8ff) to more explicit formulations of the doctrine of resurrection of the dead (Daniel 12:2; Isaiah 26:19; Ezekiel 37:1ff).

Post-Biblical Jewish literature, especially the Talmud and Midrash, contains a variety of teachings concerning the fate of the soul after death, messianic redemption *(yimot ha-mashiach)*, resurrection of the dead *(techiyat ha-meytim)*, and the world to come *(olam ha-ba)*. In the 12th century, the great physician and theologian, Maimonides, formally incorporated the Talmudic belief in resurrection into the 13 fundamental principles of Jewish faith.

Jewish mystical belief in reincarnation of the soul *(gilgul)* emerged as a major theme in Kabbalistic literature in medieval times and subsequently penetrated many areas of popular faith and custom in Jewish communities throughout Europe, Asia, and North Africa.[3] The neokabbalistic renaissance of the 16th century, which emphasized concepts of the transmigration of souls, served as a prelude to the development of Hasidism.[4]

In the United States today, there is a broad spectrum of belief among Jewish people regarding life after death. To be sure, many Jews living under the influence of modern secular culture doubt the existence of life after death. Others, however, among them Reform and Reconstructionist Jews, while unable to accept a literal belief in resurrection, do affirm some notion of the soul living on after death. Still others, especially those who follow Orthodox and Conservative liturgies and traditions, continue to affirm the traditional belief in God "who revives the dead" *(mechayeh meytim)*.

In general, we should be careful not to assume absolute correlations between affiliation with any of these modern Jewish religious movements and a personal belief or lack of belief in an afterlife. When faced with life-and-death decisions pertaining to Orthodox and non-Orthodox Jews, health care professionals would do well to follow the recommendations Dr Klessig outlines for patients from any culture—to explore their individual feelings and beliefs regarding the sanctity of life and their definition of death. In addition, it is usually helpful to encourage consultation with the family and, if appropriate, with the rabbi of their choice.

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* * *

Dr Klessig Responds

To THE EDITOR: I appreciate Dr Madorsky's comments and discussion. I believe, however, she has misinterpreted what I said in my article, "The Effect of Values and Culture on Life-Support Decisions."[1] In my paragraph on non-Orthodox Jews (p 319), when discussing possible reasons for the large contrast between Orthodox and non-Orthodox Jews, I said that the belief in an afterlife or reincarnation was not the same in non-Orthodox Jews as it is in other religions. I did not state, nor mean to imply that in Judaism there is *no* belief in some form of life continuing on after death, just that it is dissimilar from other religious beliefs. This difference may account for differences in decisions about terminating life support and was cited by several patients in the study. In her letter, Dr Madorsky actually says the same thing.

I regret if my phrasing of the sentence in question led to a misunderstanding. Perhaps the best way of looking at religious beliefs is as a framework on which people build. Although the foundations may be the same, the final product, individual religious belief systems, is very different. Thus, as I said in my article, all persons must be treated as individuals first, not as stereotyped members of a cultural group.

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REFERENCE

1. Klessig J: The effect of values and culture on life-support decisions, *In* Cross-cultural Medicine—A Decade Later [Special Issue]. West J Med 1992; 157:316-322

Correction

To THE EDITOR: I wish to point out a small error in the November issue. In the first paragraph of the excellent article on radiation retinopathy by Zamber and Kinyoun,[1] Henri Coutard's name is misspelled.

Dr Coutard is generally regarded as the father of fractionation. His landmark presentation at the International Congress of Oncology in Paris in 1922 demonstrated that laryngeal carcinoma could be successfully treated using fractionation without disastrous complications. Dr Coutard continued his work with fractionation and eventually refined his treatment schedules to the extent that they are the basis for modern radiation therapy.[2,3]

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Lessons From the Practice

Unfinished Business

DANA FREDERICK HOCH, MD, *San Jose, California*

A tall, weary-looking woman sat on the examination table and faced me, her legs crossed, her back straight. She leaned forward, a gesture of prim but faded elegance.

"All she does is follow me around. She hovers like I'm an invalid. I don't need that yet, Doctor," she said heavily.

Mrs Evans was in the clinic for a re-check, her first since the start of the radiation treatments. Her gray hair was styled in gentle curls to her shoulders, and she had brightened her pallid cheeks with rouge. She wore a flower print white blouse, simple black dress slacks, and a plain gold necklace. Her appearance bespoke a cultivated sense of style, a tenuous link to a well-mannered, comfortable past. At one time she had been quite stunning and had shown me a snapshot taken just after the war—a dramatically posed pin-up girl with raven hair, sitting on a beach towel, resting back on her outstretched arms, laughing elaborately. Now, 45 years later, her body was swiftly and malignantly decaying. There was a sorrowful contrast between reality and the aging beauty she had been and still imagined herself.

Mrs Evans had sought care two months ago for a cough and weight loss and had the kind of frightening and apathetic look one often sees on the faces of patients with cancer, before the diagnosis is made. I had been treating her for hypertension for three years before that and had tried many times to get her to stop smoking. She had spoken often of Carolyn, her daughter. Carolyn lived in a small town about 300 miles away and seldom visited or wrote, except to borrow money or cry on her shoulder. Mrs Evans complained bitterly about her daughter's insensitivity, despite all the love she had been given. I had inured myself to the stories and rarely commented on their relationship as I saw it: Disillusioned mother and ungrateful daughter spent years communicating as if they were carefully stepping through a field of emotional land mines. Mrs Evans felt used and neglected but loaned her daughter money nonetheless, out of some sense of love, guilt, and obligation. When Carolyn found out about the cancer, she moved back into the old family home with her mother.

"My daughter announced to everyone, like she was some great heroine, 'I'm going to care for my mother.' Like it was some great sacrifice. It's easy now. What about all of the past?" she asked rhetorically and began to cry through stifled sobs. A tear hung for a moment on the rim of her cheek, then fell. It trickled down the front of her chest, disappeared under a fold of the blouse, and streaked the purple hash marks the radiation therapist had left behind.

I remained silent, taking in the thick, uncomfortable air of her tragedy. "Now she says she loves me and combs my hair and strokes my forehead like I'm helpless. This false affection makes me sick, Doctor."

"Have you told her just exactly how you feel?" I asked.

"No. I don't want to upset her." Her eyes brimmed. "And it wouldn't do any good."

"Why are you afraid to upset her?" I asked curtly. "What does it matter now?"

She looked up and considered my challenge. "I guess it doesn't, really."

"You both have a final opportunity to straighten out your hassles and unfinished business and communicate with each other for once. If she resents your desire to be alone, then maybe she will have to learn what it means to be a loving daughter, and you will finally begin some honest dialogue and quit holding onto pretenses."

She fell silent, and I felt a bit embarrassed by my outburst, my first comments after listening to her gripe for years. We spent the remainder of the visit cloaked in uneasy silence, and she left the office with a terse "Goodbye, Doctor. Thank you."

Afterwards I tried to understand why I had been so upset by my patient. In part it was the pathetic years of masquerade and platitudes that would continue until she died. And then it would be too late for either of them. But more than that, I recognized myself in Mrs Evans, and it stung.

I have avoided so many opportunities to come clean with my feelings, out of fear that my words may jeopardize the status quo, with patients and family and friends. Ironically, with those I am closest to, I often struggle, like Mrs Evans, to preserve a sanitary fabrication that allows me to duck the hard issues: expressions of love and anger, disappointment, and fear of change. Mrs Evans presented me with the same challenge that I had thrown up to her. It was not too late for either of us.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Hoch DF: Unfinished business. West J Med 1993 Feb; 158:202)

From the Primary Care Division, Department of Medicine, Santa Clara Valley Medical Center, San Jose, California
Reprint requests to Dana F. Hoch, MD, 1034 Laurie Ave, San Jose, CA 95128.

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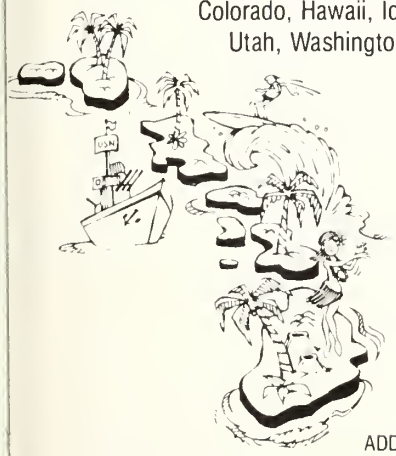

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OCCUPATIONAL/ENVIRONMENTAL

July 25-30—**Sports Medicine 1993.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

ONCOLOGY

March 4-5—**Dimensions of Caring 1993: A Symposium on Palliative Care of the Cancer Patient.** Scripps Clinic and Research Foundation at Doubletree Hotel Horton Plaza, La Jolla. Thurs-Fri. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-9592.

April 3—**Current Controversies in Breast Cancer 1993.** Good Samaritan Hospital Cancer Institute at Red Lion Hotel, San Jose. Sat. 6 hrs. Contact: Good Samaritan Cancer Institute, (408) 358-5640.

OPHTHALMOLOGY

February 26-27—**7th Annual Visions in Ophthalmology Symposium.** Mericos Eye Institute at Scripps Memorial Hospitals. Fri-Sat. 12 hrs. Contact: Sheila Seid, 3030 Children's Way, Ste 402, San Diego 92123. (619) 974-6780.

May 14-15—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OTOLARYNGOLOGY

February-April 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Sun-Fri. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

February 19-21—**Midwinter Clinical Conference for Otolaryngologists and Ophthalmologists.** Research Study Club of Los Angeles at Moseley-Salvatori Conference Center, Los Angeles. Fri-Sun. 15 hrs. Contact: Research Study Club, PO Box 1216, Murrieta 92564. (714) 677-4482.

June 23-25—**20th International Conference on Cochlear Implants.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. Contact: UCSF.

PATHOLOGY

March 13—**Update on Dialysis Access: Creation, Maintenance and Salvage.** UCSD at Le Meridien. Sat. Contact: UCSD.

March 19-20—**Pathology Forum: 1993.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 17—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-6310.

May 27-29—**9th Annual Current Issues in Anatomic Pathology: 1993.** UCSF at Mark Hopkins Intercontinental Hotel Nob Hill, San Francisco. Thurs-Sat. 19.5 hrs. $450. Contact: UCSF.

PEDIATRICS

February 15-17—**Pediatrics Update.** San Diego State University at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2297.

February 26-28—**Current Concepts in Pediatric Medicine: 1993.** Children's Hospital San Diego and American Academy of Pediatrics at Catamaran Resort Hotel, San Diego. Fri-Sun. Contact: Continuing Education, 8001 Frost St, San Diego 92123. (619) 576-4072.

February 27-28—**Stabilization and Management of the Critically Ill Child.** UCSF at Grand Hyatt on Union Square, San Francisco. Sat-Sun. Contact: UCSF.

March 22-26—**Advanced Clinical Education in Child and Adolescent Obesity.** UCSF at San Francisco. Mon-Fri. 42 hrs. $350. Contact: UCSF.

April 2-3—**Ambulatory Pediatrics: Special Spotlight Morning in Neonatology.** UCD at Sacramento Inn. Fri-Sat. 10 hrs. Contact: UCD.

April 3-10—**Pediatrics Emergencies.** UCSD at Poipu Beach Hotel and Waiohai Resort, Kauai, Hawaii. 1 wk. 21 hrs. $450. Contact: UCSD.

May 13-15—**26th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 11-13—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 14 hrs. Contact: Children's Hospital, (619) 576-4072.

PSYCHIATRY

February 27—**Sleep Apnea: New Insights into Pathophysiology and Treatment.** Scripps Clinic and Research Foundation at La Jolla. Sat. 8 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

February 27-28—**Clinical Issues of Sexual Fantasy, Compulsion, Desire, Inhibition and Eroticism.** UCLA at Dodd Hall. Sat-Sun. 10 hrs. $195-$215. Contact: UCLA Extension.

March 4-6—**51st Annual Meeting of the American Psychosomatic Society.** UCSD at Omni Hotel, San Diego. Thurs-Sat. Contact: UCSD.

March 6-7—**Basic Hypnosis: A Hands-On Workshop.** Southern California Society at Airport Marina Hotel, Los Angeles. Sat-Sun. 13 hrs. $295. Contact: Karnie Starrett, SCSCH, 10840 Queensland St, Los Angeles 90034-3426. (310) 475-1260.

April 24-25—**The Cutting Edge Conference 1993: The Treatment of Severe Personality Disorders.** UCSD at Doubletree Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

April 29-May 2—**12th Annual Child Abuse Conference.** UCD at Cancer Center Auditorium, Sacramento. Thurs-Sun. Contact: UCD.

May 14-19—**The Power of Art: Introduction to Medical Hypnosis.** UCSD at Colonial Inn, Del Mar. Fri-Mon. 26 hrs. $595. Contact: UCSD.

RADIOLOGY

February 15-19—**Diagnostic Imaging Update: Mammography, MRI, Body Imaging, Neuroradiology, Pediatrics.** Stanford University Medical Center at Ritz-Carlton, Palm Beach. Mon-Fri. 23.75 hrs. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 22-26—**Diagnostic Imaging Update.** Stanford University Medical Center at Ritz-Carlton Hotel, Kapalua Bay, Maui, Hawaii. Mon-Fri. $550. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

February 24-27—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Wed-Sat. 15 hrs. $500. Contact: UCSD.

March 8-12—**8th Annual San Diego Postgraduate Magnetic Resonance Imaging Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 29 hrs. $595. Contact: Dawne Ryals, PO Box 1925, Roswell 30077-1925. (404) 641-9773.

March 10-12—**13th Annual Radiation, Oncology, Biology and Physics.** UCSF at Hotel Nikko, San Francisco. Wed-Fri. 18 hrs. Contact: Crest Organization (415) 595-2704.

March 13—**Focus on Hemodialysis Access: Creation, Maintenance and Salvage.** American College of Emergency Physicians at Le Meridien, San Diego (Coronado). Sat. 6.5 hrs. $75. Contact: UCSD.

March 15-17—**Squaw Valley Minimally Invasive Conference for Diagnostic Radiologists and Surgeons.** UCD at Resort at Squaw Creek, Squaw Valley. Mon-Wed. 14 hrs. $295. Contact: UCD.

March 28-April 2—**General Radiology Review Course.** UCLA at Doubletree Hotel, Marina del Rey. Sun-Fri. 40 hrs. $425. Contact: UCLA Department of Radiological Sciences.

April 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sat. 20 hrs. $500. Contact: UCSD.

April 18-23—**13th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 23-24—**Imaging for Clinicians.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 24—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8.25 hrs. $135. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

June 14-18—**MRI: A State-of-the-Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, San Francisco. Mon-Fri. 27 hrs. $650. Contact: STAN.

SURGERY

February 18-23—**60th Annual Meeting of the American Academy of Orthopaedic Surgeons.** American Academy of Orthopaedic Surgeons at Moscone Center, San Francisco. Thurs-Tues. Contact: Alvin Nagelberg, (708) 384-4138.

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March 17-20—**Surgical Challenges of the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at CMG Building, La Jolla. Wed-Sat. Contact: UCSD.

March 25-26—**General Thoracic Surgery.** American College of Chest Physicians at Caesar's Palace Hotel, Las Vegas, Nevada. Thurs-Fri. 13 hrs. $325-$375. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (708) 498-1400.

March 25-27—**Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

April 15-17—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

April 18-23—**Controversial Areas in General Surgery.** UCLA at Hotel Indian Wells, Indian Wells. Sun-Fri. 16 hrs. Contact: UCLA Extension.

May 20-21—**8th Annual Neurosurgery Postgraduate Course: Intracranial Tumors—Modern Management.** UCSF at Grand Hyatt on Union Square. Tues-Thurs. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

February 19-20—**Overcoming Barriers to Health Care Interventions.** UCLA at Sunset Village Conference Center, Westwood. Fri-Sat. 15.5 hrs. $75-$150. Contact: UCLA Extension.

February 22-26—**Physician Heal Thyself.** UCSD at San Diego Princess Resort. Mon-Fri. Contact: UCSD.

March 19-20—**Annual Clinical Nutrition.** UCD at Berkeley Marina Marriott. Fri-Sat. Contact: UCD.

March 26-April 4—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. 1½ wks. Contact: UCLA Extension.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology and Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

February 22-26—**Colorado Conference on Contemporary Family Practice.** University of Colorado School of Medicine at Breckenridge. Mon-Fri. Contact: U of Colo.

February 23—**Perinatal Update.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy. (303) 270-8376.

February 26-March 1—**Principles of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Fri-Mon. Contact: U of Colo.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

February 27-March 5—**Crash '93: Colorado Review of Anesthesia.** University of Colorado School of Medicine at Radisson Resort, Vail. Sat-Fri. Contact: U of Colo.

February 27-March 6—**Horizons in Surgery.** University of Colorado School of Medicine at Beaver Run Resort, Breckenridge. Sat-Sat. Contact: U of Colo.

February 28-March 5—**ENT Ski Conference.** University of Nebraska Medical Center Continuing Medical Education Program at Keystone Resort, Keystone. Sun-Fri. Contact: Brenda C. Rani, University of Nebraska Continuing Education. (402) 559-4152.

February 28-March 5—**7th Annual Cardiology for the Clinician: Practical Guidelines for Merging Advances in Cardiology With Bedside Medicine.** University of Illinois at Snowmass. Sun-Fri. Contact: Sue Talbert, UIC Conferences and Institutes (M/C 607), Box 6998, Chicago, IL 60680. (312) 996-4631.

March DTBA—**Fifth Annual Colorado Geriatrics Overview.** University of Colorado School of Medicine at Iron Horse Resort, Winter Park. Contact: U of Colo.

March 7-10—**XXVII Aspen Conference on the Fetus and Newborn.** Children's Hospital at Aspen. Sun-Wed. Contact: Jessica White. (303) 861-6946 or (800) 225-0010.

March 11-12—**Fifth Annual Women and Addictions: Healing and Recovery in the '90s.** Mile High Council on Alcoholism and Drug Abuse. Sheraton Denver West Hotel and Conference Center. Thurs-Fri. Contact: Marywyn Germaine. (303) 825-8113.

March 12-13—**Moms at Risk/Babies at Risk.** Children's Hospital at Greeley. Fri-Sat. Contact: Mary Haley. (303) 861-6946 or (800) 225-0010.

April 1-3—**Rural Perinatal Traineeship Program.** Children's Hospital at Denver. Thurs-Sat. Contact: Outreach Office. (303) 861-6668.

April 6-7, 13-14—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy. (303) 861-6668.

April 22-24—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office. (303) 861-6668.

April 26-27—**Neonatal Resuscitation Hospital-based Instructor Course.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office. (303) 861-6668.

May 7-8—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack. (303) 861-6506.

May 10-13—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel. (303) 861-6188.

June 10-11—**Basic/Advanced Fetal Monitoring Program.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Trish Beachy. (303) 270-8376.

June 10-11—**Neonatal Resuscitation Program Provider Course.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Outreach Office. (303) 861-6668.

June 10-12—**Sixth Annual Summer in the Mountains Conference.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Sat. Contact: Mary Haley. (303) 270-8376.

June 14-16—**Community Health Traineeship Program.** Children's Hospital, Denver. Mon-Wed. Contact: Outreach Office. (303) 861-6668.

July 13—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy. (303) 270-8376.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office. (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel. (303) 861-6668.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office. (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy. (303) 270-8376.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office. (303) 861-6668.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office. (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office. (303) 861-6668.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists. (303) 449-3566.

(Continued on Page 208)

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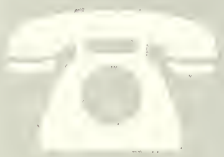

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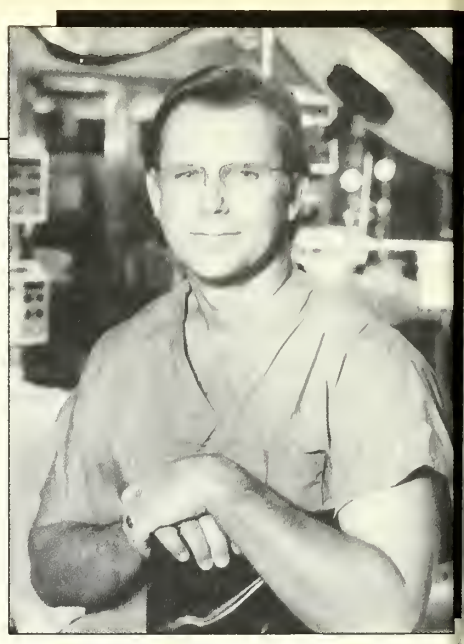

Vaughn A. Starnes, M.D. has joined the University of Southern California School of Medicine.

Vaughn A. Starnes, M.D., has joined the University o Southern California School of Medicine as Professor o Surgery, Chief of the Division of Cardiothoracic Surger and Director of the USC Cardiothoracic Center at US University Hospital, Childrens Hospital Los Angeles and Lo Angeles County+USC Medical Center. Dr. Starnes is a world recognized leader and innovator in adult and pediatric heart heart-lung and lung transplantation and treatment of congenita heart disease.

In 1984 Dr. Starnes was accepted to the Stanford Cardiothora cic program, where he completed two years as a resident in cardio vascular surgery, and one year as chief resident in cardia transplantation under the guidance of Norman Shumway, M.D.

In 1988 Dr. Starnes was appointed director of Stanford's hear lung transplantation program, and later became chief of pediatri heart surgery and director of the transplant program at Stanford Lucile Salter Packard Childrens Hospital. He performed about 40 adult and pediatric cardiac cases annually at Stanford. In additio to his adult cardiothoracic surgical expertise, Dr. Starnes earned national reputation for his work in pediatrics.

Dr. Starnes also pioneered lung and heart-lung transplant pro cedures in children that previously had only been performed o adults. In 1991 he was the first surgeon to transplant the le upper lobe of a 2-year-old donor into a newborn with pulmona hypertension who could not be weaned off ECMO (Extracorpore Membrane Oxygenation). In 1992, he performed the first lun transplant on a baby with congenital diaphragmatic hernia.

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The USC Cardiothoracic Center is one of a handful of centers in the country to provide a comprehensive range of adult and pediatric cardiovascular services including adult and pediatric heart, heart-lung and lung transplantation.

The Center features a non-invasive vascular diagnostic laboratory, diagnostic angiography laboratory and state-of-the-art cardiac catheterization laboratories. If indicated, cardiac surgeons incorporate the latest corrective surgical techniques for conditions such as ventricular and atrial arrhythmias and aortic diseases that involve aneurysms and dissections.

The Center also specializes in the treatment of infants with congenital heart defects including hypoplastic left heart syndrome, aortic valve disease, and transposition of the great vessels.

Collaboration of Specialists

At the Center, cardiologists, cardiothoracic surgeons, vascular surgeons, anesthesiologists, radiologists, interventional radiologists and allied medical professionals pool their extensive knowledge and expertise to provide patients with the full range of diagnostic and treatment alternatives.

Goal-Directed Research

As a university-based program, the Center is actively engaged in research. Specialists identify clinical problems and then seek the answer in the laboratory. Patients benefit from this link between bench and bedside, which promises to provide a better understanding of the physiology of the disease process.

Community Resource

As a vital component of the USC School of Medicine, the USC Cardiothoracic Center serves as a key educational resource for community-based and referring physicians. Physicians are encouraged to contact the Center through PACE to obtain telephone consultations, and access information regarding new patient care techniques, medications and research protocols to receive assistance with patient management concerns.

A new era is unfolding at the USC School of Medicine. We invite you to be a part of it. For more information about the USC Cardiothoracic Center, or to refer a patient, dial:
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(Continued from Page 205)

IDAHO

February 19-21—**Ada County Medical Society's 34th Annual Medical Winter Clinics—"Sandbox Summit"—A Potpourri of Pediatric Pearls.** Shore Lodge Inn, McCall. Fri-Sun. 9 hrs. $125, Idaho Medical Association members; $175, non-members. Contact: Ada County Medical Society, Box 2668, Boise 83701; Judy Barningham, (208) 336-2930, or Marie Chester, (208) 386-2135.

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 26-27—**21st Annual New Mexico Thoracic Society Lung Disease Conference.** Kachina Lodge, Taos. Fri-Sat. Contact: Billie Dytzel, NM Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

March 13-14—**Pediatric Emergency Medicine: The Wylder Lectures.** W. R. Lovelace II Education Center, Albuquerque. Sat-Sun. Contact: Steven Yabek, MD, 715 Grand Ave NE, Ste 207, Albuquerque 87102. (505) 848-3700.

March 26-27—**Decisions at the End of Life: Is Care Ever Futile?** Holiday Inn Pyramid, Albuquerque. Fri-Sat. Contact: UNM SOM

May 14-15—**New Mexico Medical Society Annual Meeting.** Society Office, Albuquerque. Fri-Sat. Contact: NMMS, 7770 Jefferson, Ste 400, Albuquerque 87109. (505) 828-0237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

February 19-23—**37th Anesthesiology Update: Anesthesia and the Nervous System.** UUSM at Snowbird Cliff Lodge. Fri-Tues. 20 hrs. $500. Contact: UUSM.

February 23-27—**Physical Medicine and Rehabilitation Update.** UUSM at Prospector Square Conference Center, Park City. Tues-Sat. 16 hrs. $350. Contact: UUSM.

February 25-27—**Pediatric Update.** UUSM at Jackson, Wyoming. Thurs-Sat. $175. Contact: UUSM.

February 28-March 3—**34th Annual OB/GYN Update.** UUSM at Yarrow Hotel, Park City. Sun-Wed. 13 hrs. $375. Contact: UUSM.

March 3-6—**Maternal Fetal Medicine Update Course.** UUSM at Yarrow Hotel, Park City. Wed-Sat. 13 hrs. $375. Contact: UUSM.

March 5-6—**Low Back and Neck Pain.** UUSM at Marriott Hotel, Salt Lake City. Fri-Sat. Contact: UUSM.

March 8-12—**Microsurgery Workshop.** UUSM at University Park Hotel, Salt Lake City. Mon-Fri. 30 hrs. $1,900. Contact: UUSM.

March 8-12—**Advances in Internal Medicine.** UUSM at Cottonwood Center, Snowbird. Mon-Fri. 20 hrs. $375. Contact: UUSM.

March 12-13—**Western Intermountain Neurological.** UUSM at University Park Hotel, Salt Lake City. Fri-Sat. 12 hrs. $75. Contact: UUSM.

March 23-26—**Family Practice Refresher Course.** UUSM at Salt Palace, Salt Lake City. Tues-Fri. 27 hrs. $450. Contact: UUSM.

April 2—**Nephrology and Hypertension.** UUSM at University Park Hotel, Salt Lake City. Fri. 7 hrs. $50. Contact: UUSM.

July 5-9—**Update in Internal Medicine.** UUSM at Olympia Hotel and Conference Center, Park City. Mon-Fri. Contact: UUSM.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

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February 19—**Healthcare Economics in the '90s.** Seattle. Fri. Contact: VMMC.

February 25-26—**A Day in the Office: Problems in Pediatric Practice 1993.** Bellevue. Thurs-Fri. Contact: Group Health. (206) 326-3441.

February 26—**Review of HIV Infections.** Tacoma. Fri. Contact: PCMS CME.

February 26-27—**Gastroenterology Update.** Spokane. Fri-Sat. Contact: Spokane Society of Internal Medicine. (509) 448-2513.

March 2—**Health Effects of Noise Exposure.** Seattle. Tues. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

March 3-6—**North Pacific Pediatric Society.** Seattle. Wed-Sat. Contact: Children's. (206) 526-2501.

March 7-10—**Prevention 2000.** Bend, Oregon. Sat-Wed. Contact: Group Health. (206) 326-3441.

March 11—**Neurotoxicology.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

March 11-12—**Internal Medicine.** Tacoma. Thurs-Fri. Contact: PCMS CME.

March 12—**Pulmonary Medicine for the Family Practitioner.** Seattle. Fri. Contact: Children's. (206) 526-2501.

March 15-25—**Physical Medicine and Rehabilitation Review.** Seattle. Mon-Wed. Contact: U/W.

March 19-20—**APLS Course.** Seattle. Fri-Sat. Contact: Washington Chapter, American College of Emergency Physicians.

March 24-26—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

March 26-27—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: Washington Academy of Eye Physicians and Surgeons. (206) 441-9762.

March 31—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

April 5-8—**Controversies and Agreements in Internal Medicine.** Maui, Hawaii. Mon-Thurs. Contact: Group Health. (206) 326-3441.

April 6-9—**Family Practice Review.** Arizona. Tues-Fri. Contact: Pacific Northwest Medical Education Institute. (206) 258-6322.

April 8-9—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

April 9—**Advances in Occupational and Environmental Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

April 16—**20th Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare. (206) 594-1221.

April 16-17—**Tacoma Surgical Club.** Tacoma. Thurs-Fri. Contact: PCMS CME.

April 23—**Terminal/Palliative Care Update.** Tacoma. Fri. Contact: PCMS CME.

April 23-24—**Clinical Allergy for the '90s.** Seattle. Fri-Sat. Contact: VMMC.

April 23-25—**Washington State Physical Therapy Association.** Seattle. Fri-Sun. Contact: Children's. (206) 526-2501.

April 28-30—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Fri. Contact: Washington Chapter, American College of Emergency Physicians. (206) 441-9762.

April 30-May 2—**Radiology Annual Meeting.** Vancouver, BC. Fri-Sun. Contact: Pacific Northwest Radiological Society. (206) 441-9762.

May 7—**Office Gynecology.** Tacoma. Fri. Contact: PCMS CME.

May 7-8—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

May 13—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute. (206) 258-6322.

May 14-15—**Northwest Spine Review Course.** Seattle. Fri-Sat. Contact: VMMC.

May 16-19—**American Thoracic Society.** San Francisco. Sun-Wed. Children's. (206) 526-2501.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare. (206) 592-1221.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

February 18-20—**Wyoming Medical Society—Winter Seminar.** Holiday Inn at Gillette. Thurs-Sat. Contact: Wyoming Medical Society, PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424.

February 25-27—**Pediatric Update.** University of Utah School of Medicine at Jackson. Thurs-Sat. $175. Contact: Univ of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City, UT 84132. (801) 581-8664.

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat. ◆

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AMBULATORY CARE/FAMILY PRACTICE. California Emergency Physicians Medical Group is a partnership of Ambulatory Care and Emergency Medicine specialists. Opportunities available for physicians who specialize in Family Practice. We have facilities in northern, central, and southern California. For more information send CV to John Gravette, 2101 Webster St, #1050, Oakland, CA 94612, or phone (800) 842-2619.

PHYSICIANS WANTED

PHYSICIANS NEEDED

The continuing growth of our service area population (now 105,000) has created an immediate need for additional BC/BE physicians in the following specialties:

- FAMILY PRACTICE
- ORTHOPEDIC SURGERY
- OTOLARYNGOLOGY
- OB/GYN

These excellent practice opportunities offer guaranteed income and a strong referral base.

112-bed full service hospital, very well equipped. Excellent ancillary services. Our service area population is now 105,000; a growing area with new businesses and a stable economy. A 30% plus growth in population and jobs is predicted for our area during 1990s.

Located in central California near Sequoia National park, Tulare offers an excellent family oriented lifestyle and all expected amenities. Beautiful homes, close to hospital and office, are affordably priced. Good schools, many community activities, and abundant recreation including golf, tennis, skiing, mountain and equestrian activities. Easy access to all California's major metropolitan and resort areas.

Contact:
Tulare District Hospital
Physician Recruiting Office
PO Box 90112
Los Angeles, CA 90009
(800) 468-2687

BC/BE INTERNIST to join busy three Internist group in Bishop, California, gateway to the eastern Sierras. Ideal location to work, live, and enjoy four season activities. Office located adjacent to hospital. Send résumés and inquiries to Joanne Crane, Office Manager, 152 Pioneer Ln, Bishop, CA 93514

BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

MONTEREY BAY. Midway between Santa Cruz and Monterey, this unpretentious community is perfect for the hiker, biker, surfer, and outdoorsperson. Medical staff is anxious to welcome additional BE/BC physicians in Family Practice, Pulmonary Medicine, Pediatrics, and Infectious Disease. Group and independent practice with call schedule which allows time for lifestyle. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

WARM AND SUNNY ARIZONA. Thomas-Davis Medical Centers, an expanding multispecialty group of 190 plus physicians, needs BC/BE Pediatrics, Internal Medicine, Family Practice, OB/GYN, Urgent Care, General Surgery, Orthopedic Surgery, Urology, and Ophthalmology physicians. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. BE/BC. Call or write Bill De Long; (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080.

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PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as locum tenens statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanente placements as well. **INTERIM PHYSICIANS, formerly Western Physicians Registry; Northern California, contact Jim Ellis, (800) 437-7676. Southern California, contact Tracy Zweig, (800) 635-3175.**

WASHINGTON STATE UNIVERSITY Health and Wellness Services seeks a Director to provide clinical and administrative leadership for a comprehensive university health care program serving a diverse student population of 16,000. MD/DO degree, Washington State license, and relevant clinical experience required; administrative experience in collegiate health services or similar managed health care setting and BC strongly preferred. Send letter of application, CV, and three references to Barbara Hammond, PhD, Chair, 300 Ad Annex, Washington State University, Pullman, WA 99164-4310. Consideration of applications will begin February 19. Anticipated start July 1, 1993. WSU is an EO/AA educator and employer. Protected group members are encouraged to apply.

THE VA MEDICAL CENTER, PRESCOTT, ARIZONA is seeking a BC/BE Internist with or without subspecialty. Regular hours. Experience with Holter monitors, treadmill testing, and/or endoscopy desirable but not necessary. Prescott is a lovely area with beautiful surroundings, clean air, pleasant lifestyle, wonderful dry four season climate. Interested physicians may call (602) 445-4860, ext 6640, or send CV to Robert Parsons, MD, Acting Chief, Medical Service, VA Medical Center, Prescott, AZ 86313. An equal opportunity employer.

PRACTICE OPPORTUNITY. GENERAL SURGERY. GENERAL SURGEON DESIRED IN THE PACIFIC NORTHWEST—BC/BE. Pullman Memorial Hospital, located on the Washington State University campus, is a progressive 42-bed Acute Care facility, with a solo or possible partnership opportunity for a General Surgeon. With a service population of 70,000, Pullman Memorial has a full complement of specialties represented in its 65 member medical staff. Pullman, Washington is uniquely located in the center of the Pacific Northwest, bounded on the west by the Snake River as it comes out of the mountains and travels to join the Columbia. The Rockies border to the east. Pullman is renowned for the virtually unlimited sporting, recreational, cultural, and educational opportunities of an urban center in a beautiful, rural setting. For more information on this multi-town opportunity, contact Pullman Memorial Hospital, NE 1125 Washington Ave, Pullman, WA 99163.

IN ALBUQUERQUE, NEW MEXICO you will discover an abundance of sunshine, breathtaking scenery, and diverse recreational and cultural pursuits! FHP, one of America's most progressive HMOs, offers you the opportunity to explore the "Land of Enchantment's" many wonders while practicing in a setting that combines a balanced lifestyle with plenty of clinical challenge. All this and a guaranteed salary and benefit package, too! We are looking for a few good BC/BE Internal Medicine physicians to join our exceptional 24 provider group. Contact Mary Consie, (800) 444-4347, or write FHP, 4300 San Mateo NE, Albuquerque, NM 87110. EOE.

MAINE FAMILY PRACTICE RESIDENCY FACULTY POSITION–full-time, one year. Possibility for permanent position with Maine-Dartmouth Family Practice Residency. Begin July 1993. 20 plus residents: medical students from Dartmouth and other schools. Instructor/Assistant Professor level. Need BC/BE Family Practitioner skilled in practicing and teaching all Family Medicine including Obstetrics. Letter of interest/CV to Daniel Onion, Director, Maine-Dartmouth Family Practice Residency, 12 E Chestnut St, Augusta, ME 04330; (207) 622-9362.

FHP® HEALTH CARE

Internal Medicine & Family Practice

As one of the most successful HMOs in the Southwest, we have two very good reasons why you should join us at FHP Health Care® in Arizona. The first is your professional life. The second is your personal life.

The professional benefits are many, including a competitive salary and an outstanding benefits package.

Personally, you'll benefit from predictable schedules - which of course you'll need, to enjoy the breathtaking beauty of Arizona.

So why choose between professional and personal satisfaction, when at FHP in Arizona, you can have both!

Call **1-800-535-4FHP** for additional information on FHP and Arizona. Or if you prefer, send your CV to: FHP Professional Staffing, P.O. Box 52078, Phoenix, AZ 85072-2078.

FHP also has opportunities available in California, Utah, New Mexico, Nevada, Guam, and Management. EOE

PHYSICIANS WANTED

BC/BE FAMILY PHYSICIAN to join five physician, two mid-three, mid-level (three Family Practitioners, one OB, one Internal Medicine, one Certified Nurse Midwife, two Physician's Assistants) busy migrant/community clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work and Emergency Room coverage. Excellent relationship with well trained BC Family Practitioners and Surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation up to 32 days per year. Public Health Service immediate loan repayment slot. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

GILROY, CALIFORNIA. BC INTERNIST to join established but growing private practice in Gilroy, California. Ideal candidate will have one to two years practice experience. Guaranteed salary and benefits. Excellent practice opportunity in this growing community. Send CV to Number 272, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PRACTITIONER with commitment to caring for the underserved, needed to join one Family Practitioner, Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs and four Family Physicians. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

PHYSICIANS WANTED

THINK ABOUT IT!! Arizona needs Primary Care physicians in several underserved areas. From northern plateaus to southern plains, both urban and rural— solo to multispecialty. Great family lifestyle, full benefits, excellent salaries. Write Bill De Long, Catalina Professional Recruiters, PO Box 12650, Tucson, AZ 85732, or call (800) 658-9166.

FAMILY PRACTICE. Community health center serving a predominantly Hispanic, underserved inner city population seeking to expand its Primary Care physician staff. Tremendous job satisfaction; San Diego lifestyle; loan repayment possible. Contact Joseph Browne, MD, Medical Director; Logan Heights Family Health Center, 1809 National Ave, San Diego, CA 92113.

PEDIATRICIAN, BC/BE, IN THE PACIFIC NORTHWEST. A two person Pediatric department in a 30 person multispecialty group practice seeks a third partner. Rural setting located between Seattle and Vancouver, British Columbia. Competitive salary and benefits program, partnership opportunity within two years. If interested send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

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(415) 882-3376

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PHYSICIANS WANTED

UNIVERSITY PSYCHIATRIST

Nine month, full-time faculty position; consulting, supervising, training, and possible graduate teaching. Begins August 15, 1993. Coordination and liaison functions within an innovative program involving Health and Wellness, Clinical Psychology, and Counseling Services units (including a Medical Psychology, doctoral level practicum and in a predoctoral internship). Working directly with patients, and consultation regarding, e.g., diagnosis and medication. Time provided for separately arranged contract at neighboring university providing similar services. Rank and salary dependent on qualifications. Qualifications: MD with specialization in Psychiatry. Licensed/eligible in Washington and Idaho. Experience in providing clinical consultation (including crisis related), supervision, and training required. Prefer individuals with interdisciplinary interest and experience (e.g. Medical Psychology and staff liaison). Send letter of application, vitae, and three names of references to Robert H. Ragatz, PhD, Counseling Services, Washington State University, Pullman, WA 99164-4130, (509) 335-2159. Application review will begin March 1, 1993 and will continue until the position is filled. Washington State University is an equal opportunity/affirmative action educator and employer. Members of ethnic minorities, women, Vietnam era or disabled veterans, persons of disability, and/or persons between the ages of 40 and 70 are encouraged to apply.

MONTEREY BAY, NORTHERN CALIFORNIA

Santa Cruz Medical Clinic, a 62 physician multispecialty group practice with an excellent reputation for innovation and excellence, is seeking BC/BE physicians in the following specialties:

- Orthopedic Surgery
- Internal Medicine
- Family Practice with OB
- Cardiology
- Family Practice without OB

Competitive salary based upon experience. Excellent fringe benefit package. Two year partnership track. Please forward letter of interest and CV to President, Santa Cruz Medical Clinic, 2025 Soquel Ave, Santa Cruz, CA 95062, or call (408) 458-5655.

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

ATTENTION ADVERTISERS:
YOU CAN MAKE THE DEADLINE!

The *new* deadline for classified advertising is
the first of the month
preceding publication.

Call: (415) 882-3376
FAX: (415) 882-3379

PRIMARY CARE IN THE PACIFIC NORTHWEST Diverse opportunities for Family Physicians in urban and rural health centers throughout Washington, Oregon, Idaho, and Alaska. Loan repayment possible. Practice where it's nearly perfect. Send CV to Sarena Seifer, MD, Northwest Regional Primary Care Association, 4154 California Ave, SW, #7, Seattle, WA 98116; (206) 932-2133.

HAWAII. FAMILY PRACTITIONER WITH OB SKILLS and Internal Medicine physician needed for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Puanani Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792. (808) 696-7081.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

PHYSICIANS WANTED

DEAR DOCTOR:

If your goals include a quality lifestyle, a dynamic medical community, excellent schools/universities, and beautiful and affordable housing, then we have the ideal practice opportunity for you!

HOLY FAMILY HOSPITAL and the MEDICAL STAFF are working together to meet the healthcare demands of our 150,000 patient population. There is an IMMEDIATE need for BC/BE physicians in the following specialties:

- FAMILY PRACTICE
- PEDIATRICS
- INTERNAL MEDICINE
- CARDIOLOGY
- ORTHOPEDICS
- GENERAL SURGERY

SPOKANE, WASHINGTON (370K metro population) is the regional Healthcare and Cultural center offering a sound economy, unlimited outdoor recreation and a mild four season climate.

CONTACT with CV to: **Nancy Chaffins**

HOLY FAMILY HOSPITAL

N. 5633 LIDGERWOOD
SPOKANE, WA 99207
(509) 482-2164
FAX: (509) 482-2187

SALT LAKE CITY–URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved, needed to join clinics in Milton-Freewater, and Hermiston, Oregon. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

INTERNAL MEDICINE. Community health center serving a predominantly Hispanic, underserved inner city population seeking to expand its Primary Care physician staff. Tremendous job satisfaction; San Diego lifestyle; loan repayment possible. Contact Joseph Browne, MD, Medical Director; Logan Heights Family Health Center, 1809 National Ave, San Diego, CA 92113.

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Chief of Disease Control

Salary $76,086 to $94,265 annually

Plus $275.00/month Health Benefit Package

Riverside County Health Services Agency, Department of Public Health is recruiting for a Chief of Disease Control to be responsible for the Disease Control Branch of the Public Health Department. To qualify candidates must possess a valid Physician's and Surgeon's Certificate issued by the State of California. And, Option I: Certification or eligibility for certification in one of the medical specialties recognized by the American Specialty Board, OR, Option II: Three years of experience as a physician in a public health care agency. (Possession of a Master's Degree in Public Health or a closely related field may be substituted for 1 year of the required experience.) Two or more years of experience working in infectious disease control in a public health setting is highly desirable. Resumes and/or County applications materials must be received no later than 5:00 p.m. Friday, March 5, 1993. For more information and application materials, contact:

Riverside County Personnel Department
Room 109
P.O. BOX 1569
Riverside, CA 92502-1569
EEO AA M/F/D/V

SAINT JOSEPH

New Mexico

Excellent opportunity for board certified or board eligible OB/GYN, Pediatric, Internal Medicine and Family Practice physicians to practice within MED-NET (Medical Network of New Mexico), an integrated health care system. Enjoy sunshine, skiing, hiking, fishing and hunting in a Southwestern lifestyle. For further information contact Anne Winter, Director of Professional Development, The St. Joseph Healthcare System, Albuquerque, New Mexico.

(505) 246-8003

(Continued from Page 212)

PHYSICIANS WANTED

FAMILY PHYSICIAN–LEWISTON, IDAHO
Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson; or call (208) 743-8416.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

CALIFORNIA–CHICO. MEDICAL DIRECTOR for busy Emergency Department with annual volume of 16,000 and growing. Successful Occupational Medicine program. The successful applicant shall be BC in Internal Medicine or Emergency Medicine, ACLS/ATLS. Guaranteed compensation with incentives. Malpractice paid. Send r sum in confidence to Administrator, Chico Community Hospital, 560 Cohasset Rd, Chico, CA 95926. FAX (916) 894-6428.

PHYSICIANS WANTED

ORTHOPEDIC SURGEON

Valley Medical Center of Fresno, a Primary teaching hospital for the University of California, San Francisco—Fresno Medical Education Program, seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position. Eligibility for a UCSF academic clinical appointment preferred. The Orthopedic Department at VMC supports a busy level one trauma center and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. Competitive salary and benefits. Central California location offers enjoyable and affordable year-round recreational living with easy mountain and coastal access.

Address inquiries to **Richard A. Lockwood, MD, Assistant Dean/Director of Medical Affairs, 445 S Cedar, Fresno, CA 93702.** Equal opportunity employer; women and minorities are encouraged to apply.

OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

FAMILY PRACTICE. Seeking Family Practice or General Practice physician for rapidly growing area in northern Arizona — Bullhead City, Arizona/Lauglin, Nevada. Opportunity unlimited. Compensation unlimited. Malpractice and health insurance. Send CV to Bullhead Medical Center, 1648 Highway 95, Bullhead City, AZ 86442, or FAX to (602) 763-1311.

PHYSICIANS WANTED

MOUNTAIN VIEW. BC/BE Family Physician to join thriving four member Family Practice group located in the heart of the Silicon Valley. Practice includes Surgery and Obstetrics. C-sections are OK. Excellent salary and benefits. Contact Dianne Higgins, MD, 253 Franklin St, Mt View, CA 94041; (415) 967-5591.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

(Continued on Page 214)

Medical Director - Radiology

Saint John's Hospital and Health Center, a premier 501-bed full-service acute care hospital in Santa Monica, California with designated Cancer, Heart, Orthopaedic and Women's Health Centers of Excellence, is seeking an enthusiastic physician leader with vision and experience to assume the ***full-time*** position of Medical Director - Radiology The successful candidate will be a recognized leader in the field of Radiology with outstanding professional credentials An ability to anticipate and successfully manage change, an aptitude to work well with others, and demonstrated entrepreneurial acumen are all talents that would be most desired.

Exceptional candidates are invited to submit a letter of interest with an accompanying *curriculum vitae* to:

Charles A. Pietrafesa, M.D., M.B.A.
Senior Vice President Medical Affairs
Saint John's Hospital and Health Center
1328 Twenty-Second Street
Santa Monica, CA 90404

Practice Made Perfect.

If you would like to find the ideal balance between private practice and managed health care, Lutheran Medical Centers of Colorado, an affiliate of Lutheran Medical Center, has the setting for you.

Working within our network of 7 family practice and occupational medical facilities, you'll experience the challenge and professional autonomy of your own private practice. At the same time, you'll enjoy the benefits of regular hours, no on-call, guaranteed compensation and minimal administrative duties. We also provide strong support and attractive incentives for you to build the practice. It's the perfect environment for you to do what you do best—practice medicine.

In addition, Colorado offers the perfect environment for a great life away from work. Breathtaking surroundings, affordable housing and a wealth of recreational and cultural activities await.

If you're a board-certified physician and you'd like to give your practice a new dimension, please call **1-800-677-6562**, fax resume/letter of interest to **(303) 425-4019**, or write **Human Resources, Dept. WJ, 8300 W. 38th Avenue, Wheat Ridge, CO 80033**. EOE.

Lutheran Medical Center

(Continued from Page 213)

PHYSICIANS WANTED

NORTHWEST REGION

Physicians needed to join a multispecialty group, partnership, or sole practice, due to the explosive population growth. BC/BE physician specialties:

- **FAMILY PRACTICE**
- **PEDIATRICS**
- **CARDIOLOGY**
- **PSYCHIATRY**
- **INTERNAL MEDICINE**
- **ORTHOPEDICS**

Excellent practice opportunities offer guaranteed income and a strong referral base.

Contact with CV to:

Kevin Malee, Healthcare Specialist
INLAND EMPIRE PERSONNEL SERVICE
BECKER' PHYSICIAN PLACEMENT
4407 N Division, Ste 500
Spokane, WA 99207
(800) 945-4066/FAX (509) 484-6317

MEDICAL DIRECTOR needed in southern Arizona for medium-sized Primary Care staff model multispecialty group. BC/BE with experience as Medical Director in multicultural patient care. Successful candidate will have some of the following qualifications: in practice seven years, demonstrated management skills and have advanced degree MHA or MPH. Call Dee Penes; (800) 658-9166, FAX CV to (602) 322-2574 or mail to CPR, PO Box 12650, Tucson, AZ 85732.

PHYSICIANS WANTED

FAMILY PRACTICE. Premier multispecialty group near Portland, Oregon has two excellent opportunities for BC/BE Family Practitioners. Join one of two satellite clinics in which Family Physicians and Physician Assistants currently practice. Superb lifestyle, abundant recreational opportunities, and generous benefits package. Send CV to Karen Stanton, c/o The Vancouver Clinic, 700 NE 87th Ave, Vancouver, WA 98664.

FAMILY PRACTICE/INTERNAL MEDICINE. Three Physicians wanted for two locations (Merced, Loma Linda areas). No administration. Six-figure salary plus monthly profit sharing, malpractice (including tail) paid, other fringes. Call Mike Buker, Administrator, Medical Advantage; (209) 383-3990, or send CV to 750 W Olive Ave, Ste 104, Merced, CA 95348.

GENERAL INTERNIST in the Pacific Northwest Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

ENDOCRINOLOGIST. Excellent opportunity to assume practice of retiring partner in Internal Medicine/Endocrinology group. Prestigious area of southern California January 1993. Salary guaranteed and partnership opportunity available. Reply to Number 277, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

OREGON. BC/BE General Internist to join 21 member Internal Medicine department of 66 physician multispecialty clinic. University town. Guaranteed salary, incentive bonus, excellent benefits. Send CV to Richard M. Rytting, MD, Medical Director, The Corvallis Clinic, PC, 3680 NW Samaritan Dr, Corvallis, OR 97330.

PHYSICIANS WANTED

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

NORTHERN CALIFORNIA. Leading Primary Care group practice affiliated with 200-bed hospital is growing. BE/BC physicians are needed in Family Practice, Internal Medicine, Pediatrics, and OB/GYN A generous salary, good benefits, and a livable practice schedule are offered. Please send your CV to Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

PUGET SOUND. BE/BC Family Practitioners to staff walk-in clinics affiliated with 100 physician multispecialty group, located 25 miles north of Seattle. Opportunity for exceptional personal and professional lifestyle. Position offers competitive salary with excellent benefits. Available winter 1992 and summer 1993. Send CV to J. G. Finley, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201

NO HURRICANES, NO EARTHQUAKES! Just fresh air and happy living in north Idaho. An opportunity for a Primary Physician, Internist, Rheumatologist, Family Practitioner, or General Practitioner to take over an established practice at a minimal cost. Well equipped office, adjoining certified lab, experienced staff. New 170-bed hospital has state-of-the-art diagnostic and treatment facilities. Located in the foothills of the Rockies, Coeur d'Alene is a town of 25,000, a center of outdoor recreation, sports, and cultural activity Please call Kelly at (208) 664-9234

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PHYSICIANS WANTED

KAISER PERMANENTE

Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Internal Medicine, most medical subspecialties, ENT, Orthopedics, Anesthesiology, and OB/GYN. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

NORTHERN CALIFORNIA. Opportunities available with Comprehensive Medical Evaluations in Sacramento, San Jose, and Monterey bay area for BC physicians in Orthopedic Surgery, Psychiatry, Internal Medicine, and subspecialties, Dermatology, Neurology, Physical Medicine/Rehabilitation, Ophthalmology,Otolaryngology, Plastic/Reconstructive Surgery and Toxicology/ Occupational Medicine, to perform forensic medical evaluations. This is an excellent opportunity to supplement income without increasing your practice overhead. Send inquiry to Terence Doyle, Comprehensive Medical Evaluations, 87 Scripps Dr, Ste 308, Sacramento, CA 95825; or call (916) 567-3411.

CALIFORNIA–THE LAST FRONTIER may be located in the foothills of the Sierra Mountains in northern California within minutes of Modesto. If you are an Internist or Family Physician who practices quality medicine and enjoys independence, please contact Ken Baker, Physician Search Group, 550 Montgomery St, #725, San Francisco, CA 94111, (800) 229-0411, FAX (415) 399-0411.

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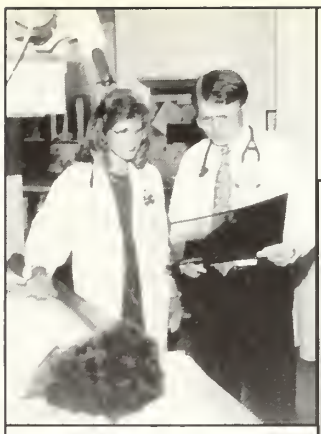

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CARDIOVASCULAR CONFERENCE AT LAKE LOUISE. March 29-April 1, 1993. Lake Louise, Alberta, Canada. Fees: $410 for ACC members; $495 for non-members; $250 for residents, fellows-in-training, nurses, and technologists. 18.5 Category 1 credit hours. For information, call American College of Cardiology; (800) 257-4739, FAX (301) 897-9745.

CARDIOLOGY FIESTA IN SAN ANTONIO. April 22-24, 1993. Hyatt Regency San Antonio, Texas. Fees: $395 for ACC members; $465 for non-members; $250 for residents, fellows-in-training, physician assistants, nurses, and technologists. For information, call American College of Cardiology; (800) 257-4739, FAX (301) 897-9745.

CARDIOLOGY FOR THE PRIMARY PHYSICIAN during Spoleto Festival USA 1993, June 1-5, 1993. The Omni Hotel, Charleston, South Carolina. Fees: $410 for ACC members; $495 for non-members; $250 for residents, fellows-in-training, physician assistants, nurses, and technologists. For information, call American College of Cardiology; (800) 257-4739, FAX (301) 897-9745.

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Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 9-11, 1993, Ritz Carlton Kapalua, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 30-October 2, 1993, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

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Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1993, Jantzen Beach, Oregon.

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WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin; the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SQ 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SQ 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin.* See WARNINGS: Skeletal Muscle.

Antipyrine: Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol. Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin: In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 5 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine: The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin: In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SQ 31,945 was not altered.

Gemfibrozil. In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SQ 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* (1 hour prior to PRAVACHOL), *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL (pravastatin sodium) was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*; a forward mutation assay in L5178Y TK +/− mouse lymphoma cells; a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL (pravastatin sodium), it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy; this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below; also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N=900)	Placebo (N=411)	Pravastatin (N=900)	Placebo (N=411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions. An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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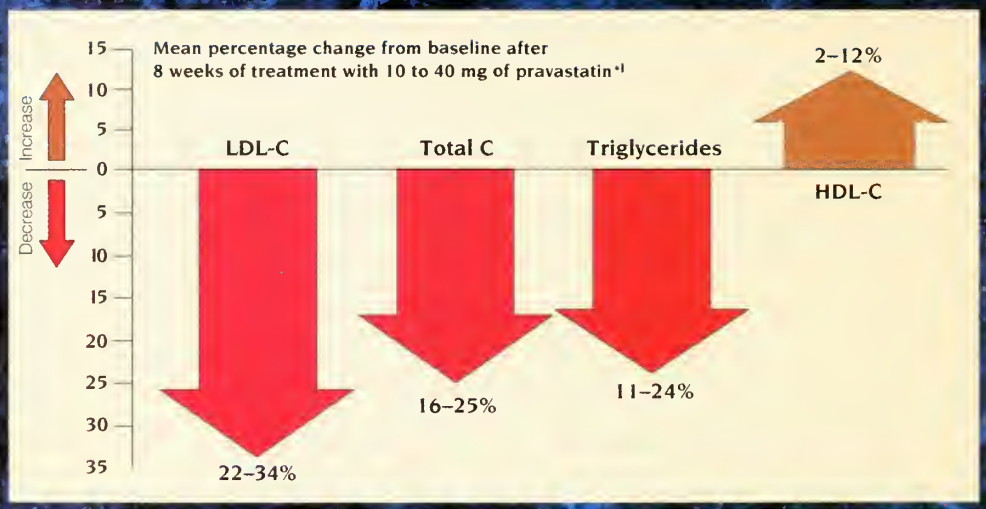

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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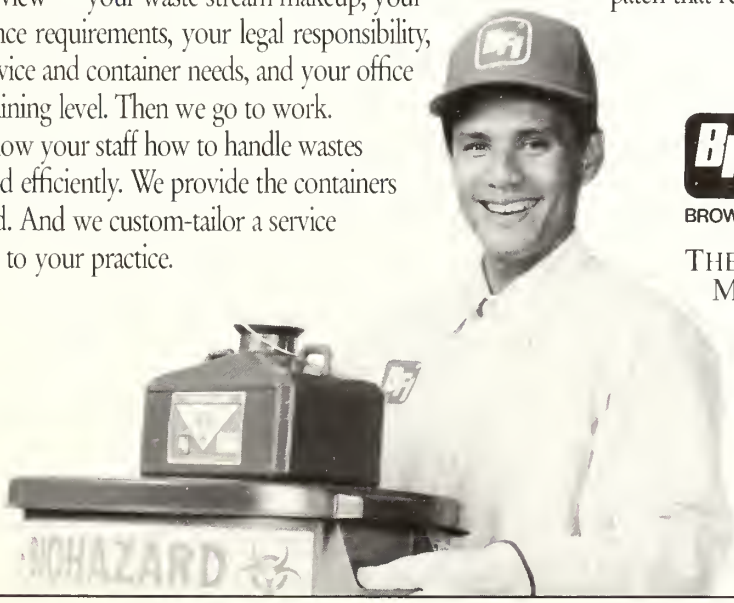

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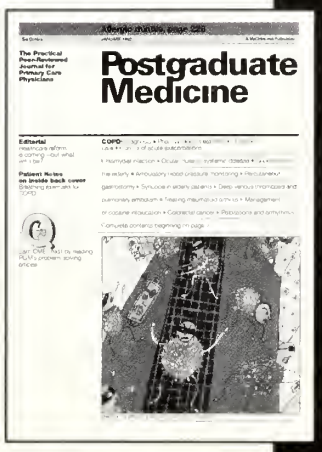

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Postgraduate Medicine

The Western Journal of Medicine

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IN HYPERTENSION—

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BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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ABSTRACTS MARCH 1993

(Andrews BT, Kenefick TP: Neurosurgical management of the acquired immunodeficiency syndrome—An update. West J Med 1993 Mar; 158:249-253)

A retrospective review of a 24-month experience on the neurosurgical service at a large metropolitan hospital identified 33 patients with the acquired immunodeficiency syndrome (AIDS) who underwent diagnostic or therapeutic procedures. Intracranial mass lesions unresponsive to empiric medical therapy for presumed *Toxoplasma gondii* encephalitis underwent diagnostic biopsy in 22 patients: primary lymphoma was identified in 10 (45%) of these patients, and biopsy led to a treatable diagnosis in 16 of the 22. Patients with lymphoma were significantly more likely to have a single mass lesion than those with other diagnoses. The remaining 11 patients had a wide variety of neurologic disorders, including multiple strokes and transverse myelitis, aspergillous fungal infection of the base of the skull, primary lymphoma of the spinal cord, cat-scratch fever of the spine causing painful radiculopathy, hydrocephalus associated with cryptococcal meningitis, and progressive inflammatory peripheral neuropathy. Two patients had lymphoma within the subarachnoid space. Three patients with well-controlled AIDS underwent elective neurosurgical therapy for intractable radiculopathies due to herniated lumbar discs in 2 and cervical spondylosis in 1.

Current treatment strategies in AIDS appear to have limited the need for brain biopsy, but the spectrum of neurologic disorders has broadened, requiring continued participation by neurologists and neurosurgeons. With improved long-term survival, the elective treatment of non–AIDS-related neurologic disorders in selected patients may be appropriate.

AIDS **AIDS NEUROPATHY**
NEUROSURGERY AND AIDS

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ABSTRACTS MARCH 1993

(Lester GW, Smith SG: Listening and talking to patients—A remedy for malpractice suits? West J Med 1993 Mar; 158:268-272)

This study evaluates the hypothesis that the way physicians communicate with patients and the degree patients perceive physician fault for bad medical outcomes are risk factors for the initiation of malpractice lawsuits. The study involved 160 adults who viewed a videotape of a physician treating a patient while using either positive or negative communication behaviors. Participants were told that the case had either a positive result, a bad result through no fault of the physician, a bad result for uncertain reasons, or a bad result that was the physician's fault. Participants then rated their litigious feelings.

Results showed that the use of negative communication behaviors by the physician increased litigious intentions. An increased perception of physician fault for the bad result also increased litigious intentions. Uncertainty as to the reason for the bad outcome, however, raised litigious feelings nearly as much as did perceived physician fault. The results of the study support the hypothesis that altering the way physicians communicate and improving patient education can affect the risk of malpractice lawsuits.

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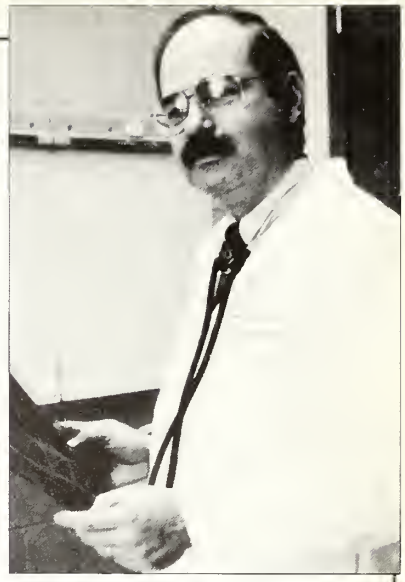

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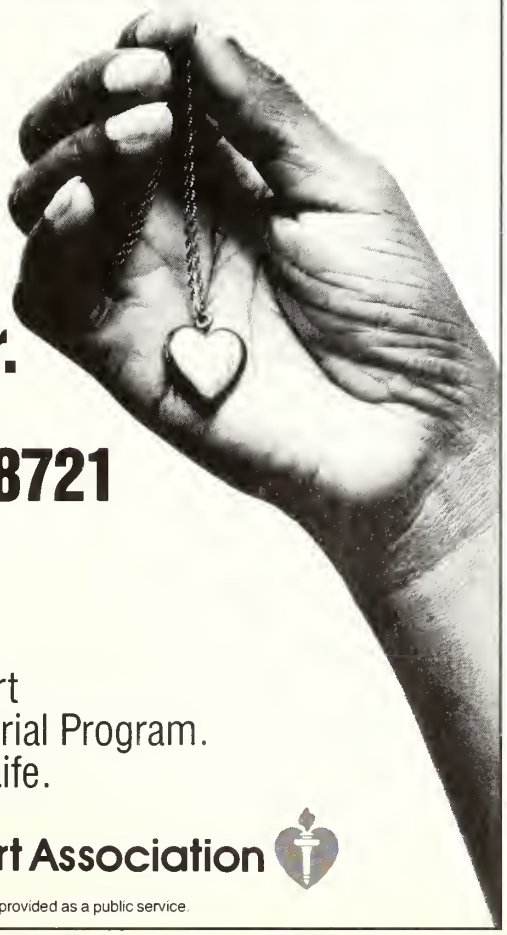

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(All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.)

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Abbreviations of journal titles should conform to those used in *Index Medicus*. List up to six authors; for seven or more, use et al after listing the first three.

1. Berman SM, Shah B, Wyle FA, Dacosta-Iyer M, McRae DM: Disseminated *Pneumocystis carinii* in a patient receiving aerosolized pentamidine prophylaxis. West J Med 1990; 153:82-86

2. Jones JS, Anderson HW Jr, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

Books

3. Berne EJ: Role playing in therapy, chap 2, Principles of Group Therapy. New York, NY, Oxford University Press, 1966, pp 35-51 (author of book is same as author of chapter)

4. Munsung JD: The role of drugs, chap 2, *In* Brest AN, Mayer JD (Eds): Hypertension—Vol 3, Therapy, 2nd Ed. Chicago, Ill, Year Book Medical Publishers, 1961, pp 456-479 (authors of book differ from chapter author)

Correspondence

5. Shusterman D: Espresso maker's wrist (Correspondence). West J Med 1990; 152:721-722

Government Publications

6. The Health Consequences of Smoking—Cardiovascular Disease: A Report of the Surgeon General. Washington, DC, US Dept of Health and Human Services publication No. (PHS) 84-50204, 1983

7. Centers for Disease Control: Update: Acquired immunodeficiency syndrome—United States. MMWR 1987; 36:522-526

Proceedings

8. O'Connell M: A Controlled Trial of Regional Intra-arterial FUDR Versus Systemic 5FU for the Treatment of Metastatic Colorectal Cancer Confined to the Liver. Presented at the annual meeting of the American Society of Clinical Oncology, San Francisco, December 1989

Mass Circulation Publications (Do not include in reference list; put in text)

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Lyme disease has been reported in red squirrels (J. Sneed, PhD, Department of Wildlife, written communication, September 1990).

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- Letter of transmittal that includes release of copyright, statement of conflict of interest, and authorship responsibility, **signed by all authors**
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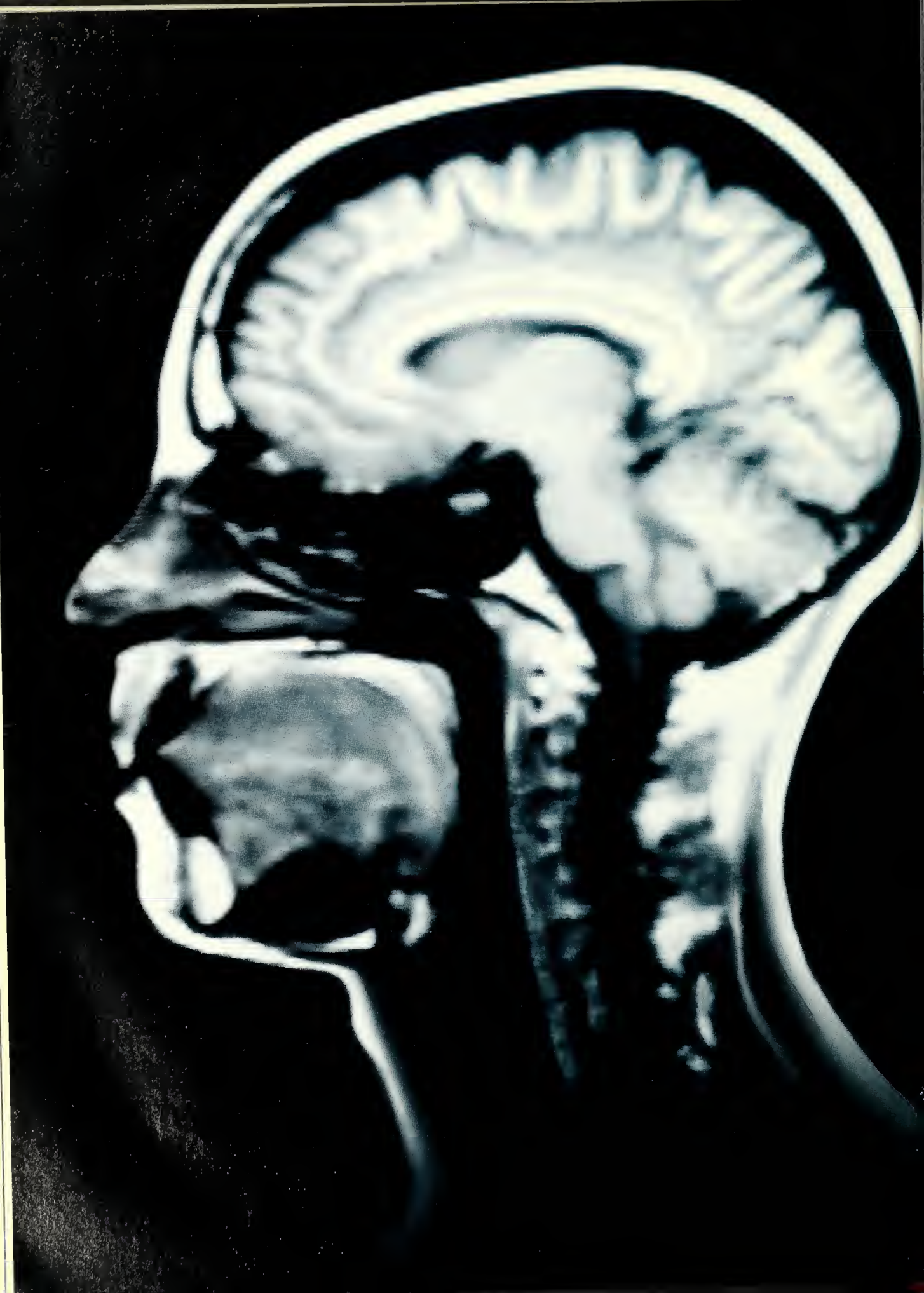
- Title page that includes current affiliation of all authors and address **and telephone number** for corresponding author
- Permission-to-borrow letters for any previously published illustrations or tables
- All references numbered consecutively, double-spaced, in *WJM* style, and cited in text. No unpublished data or nonscientific publications listed in references (include in text)



Insurance should be the last thing on your mind.

We know you didn't study medicine because you wanted to be a health benefits counselor. So CaliforniaCare® is taking steps to make sure our members have a thorough understanding of their coverage and how it works for them. We've found that people want to become informed partners in their own good health. It's a trend with which CaliforniaCare is very much in tune. So you can spend your time dealing with questions of health, not questions about insurance.

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Continuing Medical Education

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CALIFORNIA, HAWAII, AND NEVADA

This listing of continuing education programs in California, Hawaii, and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Karen Williams, Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690; or phone (415) 882-5183. For more information on accreditation or certification, please write to the above address.

ALLERGY/IMMUNOLOGY

May 7-8—**Asthma and Allergy in the 1990s.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 10 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

ANESTHESIOLOGY

March 19-23—**67th Congress of the International Anesthesia Research Society.** International Anesthesia Research Society at San Diego Marriott Hotel & Marina, San Diego. Fri-Tues. Contact: Anne Maggiore, IARS, 2 Summit Park Dr, Ste 140, Cleveland, OH 44131-2553. (216) 642-1124.

March 27-28—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Dana Point Resort, Dana Point. Fri-Sun. 9 hrs. $175-$245. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (415) 345-3269.

May 20-23—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $200. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 23-28—**Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

March 26-27—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Desert Inn, Las Vegas. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 2-3—**Cardiac Diagnostic Methods and Risk Management.** American College of Emergency Physicians at Le Meridien Hotel, San Diego. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

April 23-24—**Coronary Heart Disease Update.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

May 7-8—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Parc 55 Hotel, San Francisco. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

July 18-22—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

CARDIOVASCULAR DISEASE

March 26-28—**Thromboembolic and Primary Pulmonary Vascular Disease: Diagnosis and Management.** UCSD at Sheraton Harbor Island Hotel, San Diego. Fri-Sun. 18 hrs. $500. Contact: Shirley Kolkey, 9606 Tierra Grande, #106, San Diego 92126. (619) 271-6673.

June 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marriott Hotel, Monterey. Fri-Sun. 12 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 25-26—**Advances in Vascular Diseases.** Medical Education Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

DERMATOLOGY

July 20-24—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation and UCSD at UCSD Campus, San Diego. Tues-Sat. 36 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-31—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $435. Contact: James Graham, MD, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 9-11—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronada. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

March 15-19—**Emergency Medicine Symposia II.** UCSD at La Jolla. Mon-Fri. Contact: UCSD.

March 24-28—**Winter Wilderness Medicine: 1993.** American College of Emergency Physicians at Squaw Valley, Lake Tahoe. Wed-Sun. 21 hrs. $395. Contact: Jackie Silva, PO Box 321, Yreka 96097. (800) 888-5632.

March 31-April 3—**Advances in Emergency Medicine.** UCSF at Ritz-Carlton, San Francisco. Wed-Sat. 19 hrs. Contact: UCSF.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

(Continued on Page 235)

CONTINUING MEDICAL EDUCATION

(Continued from Page 234)

May 10-14—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 12-16—**Wound Management Workshop for Primary Care Physicians.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $475. Contact: UCSD.

June 21-25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

August 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

March 24-26—**Annual Review in Family Medicine: Controversies and Challenges in Primary Care.** UCSF at Pan Pacific Hotel, San Francisco. Wed-Fri. 15.5 hrs. $300. Contact: UCSF, Department of Family and Community Medicine.

April 10-17—**Primary Care Medicine: Update 1993.** UCSF at Maui Inter-Continental Hotel, Wailea, Hawaii. 1 week. 20 hrs. $545. Contact: UCSF.

April 17—**Ophthalmology for Primary Care.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

April 22-24—**Rheumatology for Primary Care Physicians.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 14 hrs. Contact: UCSF.

April 22-25—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 23-25—**Family Practice: Today and Tomorrow.** UCSD at San Diego Hilton. Fri-Sun. 14 hrs. $150. Contact: UCSD.

June 13-18—**17th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. $495. Contact: UCD.

July 5-8—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

July 22-24—**Primary Care for the 21st Century.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 17 hrs. $250. Contact: UCSD.

August 6-8—**Cardiology for the Family Physician and Internist.** Continuing Medical Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

HEMATOLOGY

March 17-20—**5th International Symposium on Blood Substitutes.** UCSD at Sheraton Harbor Island. Wed-Sat. Contact: UCSD.

April 25-28—**10th Scientific Meeting of the Inter-American Society of Hypertension.** UCSD at Sheraton-Grande Torrey Pines. Sun-Wed. 39 hrs. $300. Contact: UCSD.

April 28—**World Hypertension League Symposium.** UCSD at Sheraton-Grande Torrey Pines. Wed. 4 hrs. Contact: UCSD.

May 15—**Hyperlipidemia.** UCD at Sacramento. Sat. Contact: UCD.

INFECTIOUS DISEASES

March 16-18—**Planning and Evaluation HIV Programs.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 23-25—**STD/HIV for Outreach Workers.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Thurs. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

March 30-31—**HIV Update.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Tues-Wed. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

April 2-3—**Fighting for Their Lives: You Can Make a Difference—HIV Update.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 9 hrs. $130. Contact: UCD.

April 12-24—**Comprehensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. 1¾ wks. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

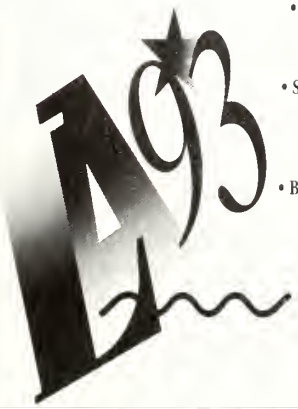
ASAM's 24th Medical-Scientific Conference
April 29 - May 2, 1993 Los Angeles, California

23 Credit Hours in Category I

The largest gathering of physicians, dedicated to the treatment, education, research and prevention on addictions...BE PART OF IT!

MAJOR CONFERENCE SESSIONS AND SYMPOSIUMS

• Ruth Fox Course for Physicians • National Forum on Aids
• Distinguished Scientist Lecturer with Guest Lecturer: Floyd E. Bloom, *M.D., Chairman and Member, Department of Neuropharmacology, The Scripps Research Institute*
• Psycho/Social Treatments and Pharmacaotherapeutic Interventions
• Needle Supply and Other Harm Reduction Strategies Regarding Drug Use
• Recent Advances in Perinatal Addiction
• Strengthening the Linkage Between Primary Care and Substance Abuse Treatment
• Bio-Behavioral Correlates of Relapse in the Addictions
• Brief Interventions for Alcohol use Problems
• Prevention of Alcohol Problems
• Research for Motivation for Treatment
Benzodiazepine Dependence and Addiction
• Are There Addictions or Just Other Types of Problems?
• Adolescence and Smoking



ASAM

Call or write today to:
AMERICAN SOCIETY OF ADDICTION MEDICINE
5225 Wisconsin Ave., NW, Suite 409 Washington, DC 20015
Fax: 202/537-7252 202/244-8948

April 28-30—**Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. Contact: UCSF.

May 21—**7th Annual AIDS Conference: HIV at the Crossroads—The Problems and the Promises.** Alta-Bates Medical Center at Parc Oakland Hotel, Oakland. Wed. 7 hrs. $120. Contact: Carolyn Lowery or Mary Grim, (510) 204-1590.

May 24-29—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Sat. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

INTERNAL MEDICINE

March 15-17—**Lake Tahoe Annual Vascular Conference.** UCD at Resort at Squaw Creek, Olympic Village. Mon-Wed. 14 hrs. $295. Contact: UCD.

March 19-25—**Internal Medicine 1993: A Comprehensive Review.** Sharp Memorial Hospital at Hotel del Coronado, San Diego. Fri-Tues. 54 hrs. $695. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 5-8—**Controversies and Agreements in Internal Medicine.** Group Health Cooperative at Intercontinental Hotel, Maui, Hawaii. Mon-Thurs. 19 hrs. $425. Contact: GHC, CX5, 201 16th Ave East, Seattle, WA 98112. (206) 326-3441.

NEUROLOGY

May 14-16—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sun. 12 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

June 12-14—**Pharmacological Approaches to the Treatment of Chronic Pain: Current Concepts and Critical Issues.** UCSF at Doubletree Fisherman's Wharf, Monterey. Sat-Mon. Contact: UCSF.

August 5-7—**5th Annual New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. 14 hrs. $350. Contact: UCSD.

(Continued on Page 242)

(Continued from Page 224)

286 **Long-Range Safety and Protective Benefits of Angiotensin-Converting Enzyme Inhibitors for Hypertension—Do We Need More Clinical Trials?**

Moderator: MOHINDER P. SAMBHI, MD, PhD
Discussants: HARALAMBOS GAVRAS, MD; J. I. S. ROBERTSON, MD; and WILLIAM McFATE SMITH, MD, MPH

An edited summary of an Interdepartmental Dean's Conference arranged by the Department of Medicine of the University of California, Davis, School of Medicine and Department of Veterans Affairs, Martinez Medical Center, Martinez, California. The permanent chair and organizer of these conferences is Michael C. Geokas, MD, PhD, Professor of Medicine and Biological Chemistry (Emeritus).

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Pathology

Items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

295 **Human Prion Diseases**
KARL H. ANDERS, MD

295 **Hepatitis C Screening and Blood Safety**
KATHLEEN SAZAMA, MD, JD

296 **Acquired Immunodeficiency Syndrome Vaccines**
MURRAY B. GARDNER, MD

297 **Laboratory Evaluation of Inherited Thrombotic Disorders**
GEORGE M. RODGERS, MD, PhD

297 **Enhancing Antibody and Its Role in Acquired Immunodeficency Syndrome**
W. EDWARD ROBINSON, Jr, MD, PhD

298 **Iron Deficiency**
EDWARD LARKIN, MD

299 **Molecular Techniques**
WAYNE W. GRODY, MD, PhD

ALERTS, NOTICES, AND CASE REPORTS

300 **Eosinophilic Meningitis Associated With Coccidioidomycosis**
YAHYA ISMAIL, MD, and EDWARD L. ARSURA, MD

From the Central California Heart Institute, Department of Medicine, Kern Medical Center, Bakersfield, and the Department of Medicine, University of California, Los Angeles, School of Medicine.

301 **Successful Medical Treatment of an Infected Prosthetic Aortic Graft**
PRISCILLA SIOSON, MD, and RICHARD B. BROWN, MD

From the Infectious Disease Division, Baystate Medical Center, Springfield, and Tufts University School of Medicine, Boston, Massachusetts.

(Continued on Page 244)

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

In hypertension or angina therapy

CONSIDER THE CARDIOVASCULAR ENVIRONMENT

INTRODUCING ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

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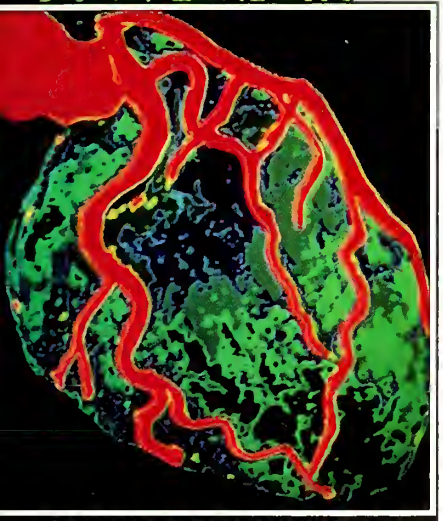
Please see brief summary of prescribing information on last page of this advertisement.

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

Hypertension or angina control

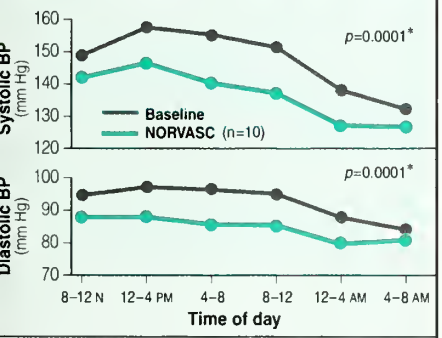
THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

Please see brief summary of prescribing information on last page of this advertisement.



Digital subtraction angiography of the heart

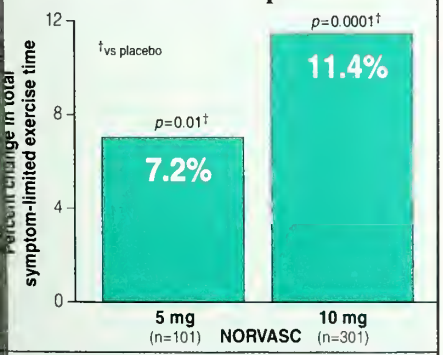
Mean blood pressure (BP) over 24 hours (week 4 data)[1]



Results of a double-blind, randomized, parallel, placebo-controlled study of NORVASC on ambulatory BP in 15 evaluable hypertensive patients (diastolic BP range: 95 to 114 mm Hg): 10 on NORVASC, 5 on placebo. A 4-week, single-blind, placebo run-in period was followed by 4 weeks of double-blind therapy. Ambulatory BP was measured for 24 hours at the end of the placebo run-in phase and after double-blind therapy. (Data on file.[1])

* Average of mean BP values over 24 hours at week 4 versus baseline averages

Change in symptom-limited exercise time measured 24 hours postdose[1]



Data from eight placebo-controlled, double-blind, randomized studies of the effect of NORVASC on symptom-limited exercise time. All studies included a 2-week, single-blind, placebo run-in period. The eight studies included five monotherapy trials and three add-on therapy trials. Treatment ranged from 3 to 6 weeks. Placebo group (n=297) had a 2.1% increase in symptom-limited exercise time. Exercise time at baseline: placebo, 480 sec; 5 mg, 523 sec; 10 mg, 493 sec. (Data on file.[1])

New for Hypertension or Angina

NORVASC, a calcium channel blocker (CCB), provides effective yet gentle 24-hour control with intrinsic once-daily dosing[1]

EFFICACY

Effective for mild, moderate, and severe hypertension[1]

- Over 80% of patients responding to NORVASC are controlled on 5 mg[1]
- 92% of patients remained on NORVASC for 1 year in a long-term study[2]

Effective for chronic stable and vasospastic angina[1]

- 24-hour angina protection, including the morning hours[1]
- Effective alone or in combination with beta blockers

SAFETY

Gradual onset of action and minimal adverse effects

- No clinically significant effects on heart rate[1] or cardiac conduction[1]; no negative inotropic effects at clinical doses in hemodynamic studies,‡ even when administered with beta blockers to humans[1]
- Has been used safely in patients with concomitant diseases
  —Chronic obstructive pulmonary disease, well-compensated Class II–III congestive heart failure (CHF),§ peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles[1]
- Neutral effect on lipids[1]; no impairment of normal renal function[1]

Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects[1]

- The most common side effects are headache and edema

‡Similar hemodynamic findings, however, have been observed with agents possessing significant negative inotropic effects.
§Therapy should be initiated with caution. See PRECAUTIONS section of brief summary.

NEW, ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

NEW ONCE-DAILY NORVASC® (amlodipine besylate)...

Hypertension or angina control

THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

- No drug interaction with digoxin, warfarin, or cimetidine[1]
- Well tolerated: only 1.5% of patients in placebo-controlled trials (n=1730) discontinued NORVASC due to adverse effects[1]

Dose-related side effects

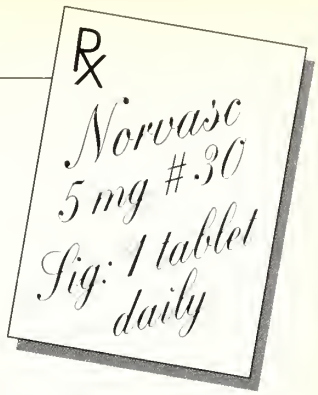
Adverse event	NORVASC (%) 5 mg (n=296)	NORVASC (%) 10 mg (n=268)	placebo (%) (n=520)
Edema	3.0	10.8	0.6
Dizziness	3.4	3.4	1.5
Flushing	1.4	2.6	0.0
Palpitation	1.4	4.5	0.6

Please see brief summary of prescribing information on last page of this advertisement.

DOSING

Intrinsic once-daily dosing

- The usual starting dose is 5 mg in angina or hypertension
  - —In hypertension, small, fragile, or elderly individuals or patients with hepatic insufficiency may be started on 2.5 mg once daily
- Titration can proceed to 10 mg
  - —Most angina patients will require 10 mg
- Can be taken with or without food



NEW, ONCE-DAILY

5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)

CONFIDENT 24-HOUR CONTROL THAT CONSIDERS THE CARDIOVASCULAR ENVIRONMENT

References:

1. Data on file. Pfizer Inc, New York, NY.
2. The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med* 1991;151:1413-1423.

Brief Summary
NORVASC® (amlodipine besylate) Tablets
For Oral Use

CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine

WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase The mechanism of this effect has not been elucidated

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in NYHA Class II-III heart failure patients have shown that NORVASC did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure. In general, all calcium channel blockers should be used with caution in patients with heart failure

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of the beta-blocker

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (t ½) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis)

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: It is not known whether amlodipine is excreted in human milk In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows. edema (1 8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0 6% placebo); dizziness (1.1% at 2.5 mg. 3 4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo), flushing (0 7% at 2 5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2 5 mg. 1 4% at 5 0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1 4%, compared with 0.6% placebo)

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows edema (5 6% in men, 14 6% in women, compared with a placebo incidence in men of 1.4% and 5 1% in women); flushing (1 5% in men, 4 5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0 9% in men and 0.9% in women), and somnolence (1 3% in men, 1 6% in women, compared with a placebo incidence of 0 8% in men and 0.3% in women)

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain, they are listed to alert the physician to a possible relationship **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, **central and peripheral nervous system:** hypoesthesia, paresthesia tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting, **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia. **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis. **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus, **urinary system:** micturition frequency, micturition disorder, nocturia, **autonomic nervous system:** dry mouth, sweating increased, **metabolic and nutritional:** thirst, **hemopoietic:** purpura

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized, another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg) During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted Frequent blood pressure measurements are essential Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg
**These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

More detailed professional information available on request
Revised August 1992

Pfizer

Pfizer Labs

(Continued from Page 235)

OB/GYN

March 18-20—**Prevention of Prematurity and Neonatal Mortality.** UCSD at Loew's Coronado. Thurs-Sat. 13 hrs. $370. Contact: UCSD.

March 27—**Advanced Laparoscopy Including Laparoscopy-Assisted Vaginal Hysterectomy.** Beverly Hills Medical Center, Los Angeles. Sat. 7 hrs. Contact: Education Design, 5925 E Evans, Ste 200 C, Denver, CO 80222. (800) 832-5115.

April 14-18—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Susan Butler, PCFS, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (310) 947-7068.

OCCUPATIONAL/ENVIRONMENTAL

July 26-30—**Sports Medicine 1993.** UCSD at San Diego Princess Resort. Mon-Fri. 21 hrs. $350. Contact: UCSD.

ONCOLOGY

April 3—**Current Controversies in Breast Cancer 1993.** Good Samaritan Hospital Cancer Institute at Red Lion Hotel, San Jose. Sat. 6 hrs. Contact: Good Samaritan Cancer Institute, (408) 358-5640.

OPHTHALMOLOGY

May 14-15—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 22—**Annual Research Symposium in Ophthalmology.** UCD at Cancer Auditorium, Sacramento. Sat. Contact: UCD.

ORTHOPAEDICS

May 1—**Shoulder Problems in the Throwing Athlete.** American Academy of Orthopaedic Surgeons at Sheraton Los Angeles Airport Hotel. Sat. Contact: AAOS.

May 19-22—**The Wrist: Problems and Challenges.** American Academy of Orthopaedic Surgeons at the Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: AAOS, Course Operations, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

June 16-19—**10th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Rebecca Rimmer, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

OTOLARYNGOLOGY

March-June 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Sun-Fri. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

June 23-25—**20th International Conference on Cochlear Implants.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. Contact: UCSF.

PATHOLOGY

March 19-20—**Pathology Forum: 1993.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 17—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-6310.

May 27-29—**9th Annual Current Issues in Anatomic Pathology: 1993.** UCSF at Mark Hopkins Intercontinental Hotel Nob Hill, San Francisco. Thurs-Sat. 19.5 hrs. $450. Contact: UCSF.

June 1-5—**Non-Gynecologic Cytopathology.** American Society of Clinical Pathologists at San Francisco. Tues-Sat. Contact: 2100 W Harrison St, Chicago, IL 60612-3798. (312) 738-1336.

August 7-14—**14th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Kapalua, Maui, Hawaii. 1 wk. Contact: UCSF.

PEDIATRICS

March 22-26—**Advanced Clinical Education in Child and Adolescent Obesity.** UCSF at San Francisco. Mon-Fri. 42 hrs. $350. Contact: UCSF.

April 1-4—**Pediatrics in Yosemite.** Valley Children's Hospital at Yosemite National Park. Thurs-Sun. 12 hrs. $370-$425. Contact: Yosemite Conference Information, (800) 548-5431.

April 2-3—**Ambulatory Pediatrics: Special Spotlight Morning in Neonatology.** UCD at Sacramento Inn. Fri-Sat. 10 hrs. Contact: UCD.

April 3-10—**Pediatrics Emergencies.** UCSD at Poipu Beach Hotel and Waiohai Resort, Kauai, Hawaii. 1 wk. 21 hrs. $450. Contact: UCSD.

May 13-15—**26th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 6—**Pediatric Pathology.** California Tumor Tissue Registry at Westin Mission Hills Resort, Rancho Mirage. Sun. 8 hrs. Contact: CTTR, c/o Loma Linda School of Medicine, AH 335, Loma Linda 92350. (909) 824-4788.

June 11-13—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 14 hrs. Contact: Children's Hospital, (619) 576-4072.

PSYCHIATRY

April 24-25—**The Cutting Edge Conference 1993: The Treatment of Severe Personality Disorders.** UCSD at Doubletree Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

April 29-May 2—**12th Annual Child Abuse Conference.** UCD at Red Lion Inn, Sacramento. Thurs-Sun. 12 hrs. $175. Contact: UCD.

May 14-19—**The Power of Art: Introduction to Medical Hypnosis.** UCSD at Colonial Inn, Del Mar. Fri-Mon. 26 hrs. $595. Contact: UCSD.

August 13-18—**The Power of Art: Introduction to Medical Hypnosis.** UCSD at Colonial Inn, Del Mar. Fri-Wed. 26 hrs. $595. Contact: UCSD.

RADIOLOGY

March 15-17—**Squaw Valley Minimally Invasive Conference for Diagnostic Radiologists and Surgeons.** UCD at Resort at Squaw Creek, Squaw Valley. Mon-Wed. 14 hrs. $295. Contact: UCD.

March 20-21—**Breast Imaging.** UCSF at Fairmont Hotel, San Francisco. Sat-Sun. 15 hrs. $340. Contact: UCSF.

March 20-22—**Breast Imaging Update.** UCSF at Fairmont Hotel, San Francisco. Sat-Mon. 17 hrs. $375. Contact: UCSF.

March 22-26—**36th Annual Diagnostic Radiology Postgraduate Course.** UCSF at Fairmont Hotel, San Francisco. Mon-Fri. 33 hrs. $595. Contact: UCSF.

March 28-April 2—**General Radiology Review Course.** UCLA at Doubletree Hotel, Marina del Rey. Sun-Fri. 40 hrs. $425. Contact: UCLA Department of Radiological Sciences.

April 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sat. 20 hrs. $500. Contact: UCSD.

April 18-23—**13th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 23-24—**Imaging for Clinicians.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 24—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8.25 hrs. $135. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

June 14-18—**MRI: A State-of-the-Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, San Francisco. Mon-Fri. 27 hrs. $650. Contact: STAN.

RISK MANAGEMENT

April 20-21—**High Risk Emergency Medicine: Preventing Malpractice.** Kaiser Permanente Emergency Medical Group at San Francisco. Tues-Wed. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

May 5-6—**High Risk Emergency Medicine: Preventing Malpractice.** Emergency Medical Group at Palm Springs. Wed-Thurs. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

June 14-16—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at Honolulu, Hawaii. Mon-Wed. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

July 19-20—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at San Diego. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

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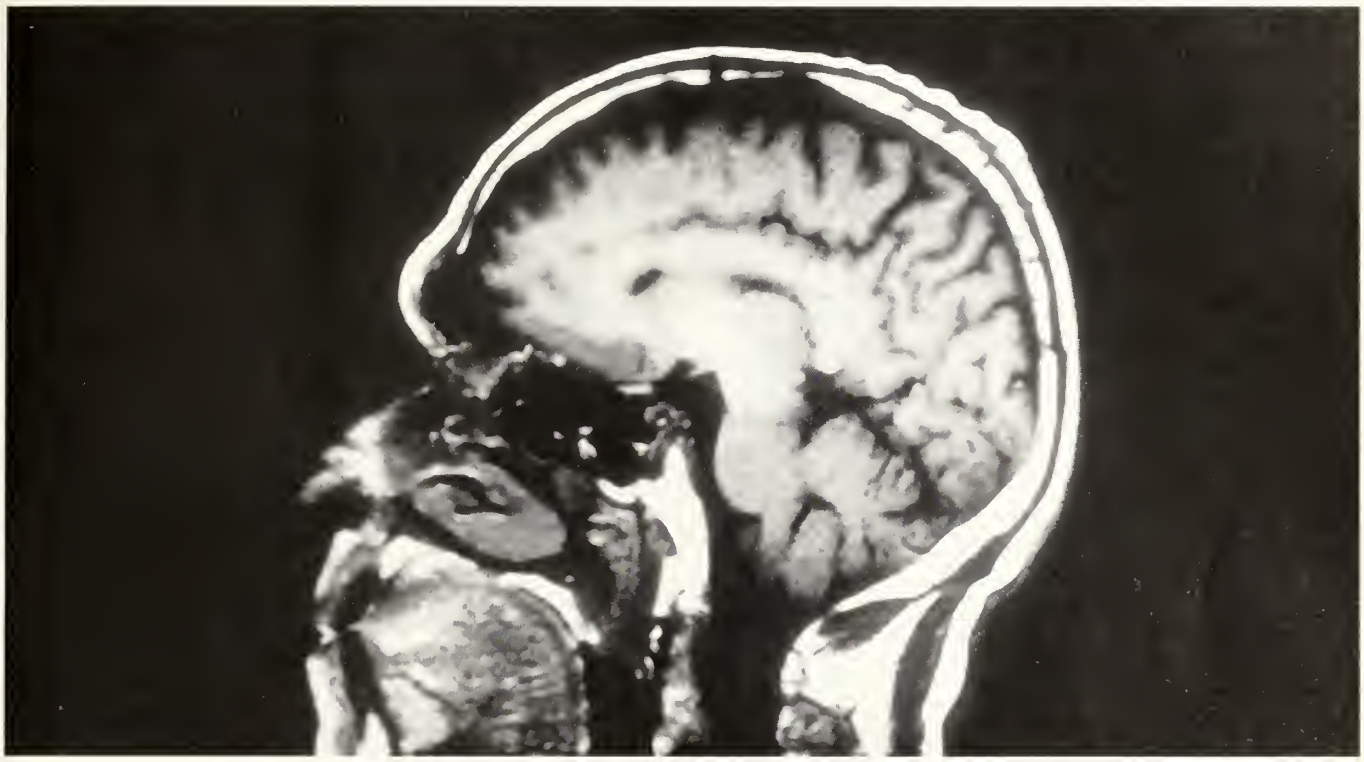
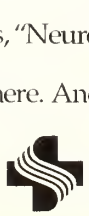
YOU DON'T HAVE TO BE A BRAIN SURGEON TO APPRECIATE OUR NEUROSCIENCE CENTER, BUT IT HELPS.



When we asked Dr. Cully Cobb why he routinely performs neurosurgery at Sutter General Hospital, he explained, "Neurosurgery has become very complex. Multiple specialities overlap and are interdependent. To provide optimal care, a physician needs a full range of services. Sutter General is one of the few hospitals that offer that kind of support." In fact, Sutter Neuroscience Center at Sutter General Hospital is the only private facility in the region that offers such a wide array in the way of neurology services. Interventional neuroradiology, angiography and neuropathology are available, along with comprehensive epilepsy services and advanced neurodiagnostics, including intraoperative studies. The six-bed Neuro Observation Unit lets physicians monitor patients' neurologic status, including EEG and intracranial pressure, around the clock. The nursing staff is specially trained in neuroscience. And neuro rehabilitation specialists provide ongoing care for patients. As Dr. Cobb puts it, "Many centers emphasize only one area. At Sutter General, there's excellence in every aspect of neurosurgical care. The equipment is top-notch. The facilities are excellent. There are superb physicians. And the operating room and neuroscience staff is outstanding." Then he adds, "Neurosurgery is like a gigantic jigsaw puzzle. If one part is missing, it's a disaster. At Sutter General, all the parts are there. And they work together beautifully." For more information about available services, call Sutter Neuroscience Center at Sutter General Hospital in Sacramento, (916) 733-3049.

Cully Cobb, M.D.



Sutter Neuroscience Center

SUTTER GENERAL HOSPITAL

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Dr Osborn is Dean and Professor of Epidemiology, School of Public Health, and Professor of Pediatrics and Communicable Diseases, Medical School, University of Michigan, Ann Arbor. She chairs the United States National Commission on AIDS.

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Dr Bazell is in private practice in San Francisco and Berkeley, California.

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Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

How Supplied: Oral tablets of YOCON® 1/12 gr. 5.4mg in bottles of 100's NDC 53159-001-01, 1000's NDC 53159-001-10 and Blister-Paks of 30's NDC 53159-001-30

References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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SURGERY

March 17-20—**Surgical Challenges of the Head and Neck: A Dissection Course Emphasizing Contemporary Strategies.** UCSD at CMG Building, La Jolla. Wed-Sat. Contact: UCSD.

March 25-26—**General Thoracic Surgery.** American College of Chest Physicians at Caesar's Palace Hotel, Las Vegas, Nevada. Thurs-Fri. 13 hrs. $325-$375. Contact: ACCP, PO Box 93826, Chicago, IL 60673. (708) 498-1400.

March 25-27—**Symposium on Aesthetic Surgery of the Face.** UCSF at San Francisco. Thurs-Sat. Contact: UCSF.

April 15-17—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. Contact: UCSF.

April 18-23—**Controversial Areas in General Surgery.** UCLA at Hotel Indian Wells, Indian Wells. Sun-Fri. 16 hrs. Contact: UCLA Extension.

May 20-21—**8th Annual Neurosurgery Postgraduate Course: Intracranial Tumors—Modern Management.** UCSF at Grand Hyatt on Union Square. Tues-Thurs. Contact: UCSF.

GENERAL/MULTIDISCIPLINARY

March 12-13—**Annual Clinical Nutrition.** UCD at Berkeley Marina Marriott. Fri-Sat. 9 hrs. $225. Contact: UCD.

March 26-April 4—**Medical Acupuncture for Physicians.** UCLA at Holiday Inn Bay View Plaza Hotel, Santa Monica. 1½ wks. Contact: UCLA Extension.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology and Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

April 1-3—**Rural Perinatal Traineeship Program.** Children's Hospital at Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

April 6-7, 13-14—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 861-6668.

April 22-24—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

April 26-27—**Neonatal Resuscitation Hospital-based Instructor Course.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6668.

May 7-8—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack, (303) 861-6506.

May 10-13—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6188.

June 10-11—**Basic/Advanced Fetal Monitoring Program.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Trish Beachy, (303) 270-8376.

June 10-11—**Neonatal Resuscitation Program Provider Course.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Outreach Office, (303) 861-6668.

June 10-12—**Sixth Annual Summer in the Mountains Conference.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Sat. Contact: Mary Haley, (303) 270-8376.

June 14-16—**Community Health Traineeship Program.** Children's Hospital, Denver. Mon-Wed. Contact: Outreach Office, (303) 861-6668.

July 13—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761

IDAHO

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 19-20—**The Medical/Surgical Approach to Arthritis of Hand and Foot.** Howard Johnson Plaza Hotel, Albuquerque. Fri-Sat. Contact: George Dixon, MD, 1020 Green Valley Rd NW, Albuquerque 87107. (505) 344-1234.

March 26-27—**Decisions at the End of Life: Is Care Ever Futile?** Holiday Inn Pyramid, Albuquerque. Fri-Sat. Contact: UNM SOM.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

(Continued on Page 314)

In Memoriam

California Medical Association

CHABANOFF, ELIZABETH, San Francisco. Died Nov 3, 1992, aged 84. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1933. Licensed in California in 1934. Dr Chabanoff was a member of the San Francisco Medical Society.

GILFILLAN, RUTHERFORD, San Francisco. Died Nov 27, 1992, aged 77. Graduate of State University of New York at Buffalo, 1941. Licensed in California in 1948. Dr Gilfillan was a member of the San Francisco Medical Society.

HARRINGTON, DONALD C., Pioneer. Died Jan 14, 1993, aged 81. Graduate of University of California, San Francisco, School of Medicine, 1939. Licensed in California in 1939. Dr Harrington was a member of the San Joaquin County Medical Society.

JAMES, WILLIAM J., Ventura. Died Dec 26, 1992, aged 81. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1937. Licensed in California in 1958. Dr James was a member of the Ventura County Medical Society.

MANN, J. DONALD, Santa Maria. Died Jan 3, 1993, aged 61. Graduate of University of California, San Francisco, School of Medicine, 1965. Licensed in California in 1966. Dr Mann was a member of the Santa Barbara County Medical Society.

MYERS, CORTLAND, Corona del Mar. Died Nov 24, 1992, aged 69. Graduate of University of Southern California School of Medicine, Los Angeles, 1949. Licensed in California in 1949. Dr Myers was a member of the Orange County Medical Association.

PAYTON, SARAH E., Sacramento. Died Dec 14, 1992, aged 61. Graduate of Howard University College of Medicine, Washington, DC, 1957. Licensed in California in 1959. Dr Payton was a member of the Sacramento-El Dorado Medical Society.

PERRY, JOHN FLECK, Gilroy. Died Dec 26, 1992, aged 74. Graduate of University of New York at Buffalo Medical School, 1951. Licensed in California in 1956. Dr Perry was a member of the Santa Clara County Medical Association.

SCHULEIN, VERNON E., San Jose. Died Dec 29, 1992, aged 73. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1942. Licensed in California in 1953. Dr Schulein was a member of the Santa Clara County Medical Association.

SNIVELY, SUZANNE A., Sacramento. Died Dec 8, 1992, aged 74. Graduate of University of Minnesota Medical School, Minneapolis, 1950. Licensed in California in 1953. Dr Snively was a member of the Sacramento-El Dorado Medical Society.

STERNER, JAMES H., Laguna Hills. Died Oct 26, 1992, aged 88. Graduate of Harvard Medical School, Boston, Massachusetts, 1932. Licensed in California in 1975. Dr Sterner was a member of the Orange County Medical Association.

TOGASAKI, KAZUE, San Francisco. Died Dec 17, 1992, aged 95. Graduate of Medical College of Pennsylvania, Philadelphia, 1933. Licensed in California in 1933. Dr Togasaki was a member of the San Francisco Medical Society.

TRAINOR, MICHAEL P., Laguna Niguel. Died Nov 29, 1992, aged 47. Graduate of University of New Mexico School of Medicine, Albuquerque. Licensed in California in 1975. Dr Trainor was a member of the Orange County Medical Association.

WATANABE, ROBERT, Los Angeles. Died Sep 30, 1992, aged 66. Graduate of University of California, Los Angeles, School of Medicine, 1955. Licensed in California in 1956. Dr Watanabe was a member of the Los Angeles County Medical Association.

WENDT, DOUGLAS D., San Jose. Died Dec 5, 1992, aged 80. Graduate of Stanford University School of Medicine, 1937. Licensed in California in 1937. Dr Wendt was a member of the Santa Clara County Medical Association.

WIKLER, IRVING, Oakhurst. Died Nov 8, 1992, aged 71. Graduate of Ohio State University, Columbus, 1948. Licensed in California in 1956. Dr Wikler was a member of the Fresno-Madera Medical Society.

Idaho Medical Association

BROWN, HAROLD W., Nampa. Died Dec 26, 1992, aged 65. Graduate of University of Washington School of Medicine, Seattle, 1956. Licensed in Idaho in 1961. Dr Brown was a member of the Southwestern Idaho District Medical Society.

DUNN, RONALD E., Moscow. Died Dec 25, 1992, aged 57. Graduate of George Washington University, Washington, DC, 1961. Licensed in Idaho in 1968. Dr Dunn was a member of the North Idaho District Medical Society.

MERRELL, ORVILLE E., Boise. Died Dec 7, 1992, aged 72. Graduate of Temple University, Philadelphia, Pennsylvania, 1948. Licensed in Idaho in 1949. Dr Merrell was a member of the Ada County Medical Society.

TRUXAL, ALBERT CARTER, Rupert. Died Dec 26, 1992, aged 74. Graduate of Jefferson Medical College, Philadelphia, Pennsylvania, 1944. Licensed in Idaho in 1944. Dr Truxal was a member of the Mini-Cassia District Medical Society.

VYCITAL, RICHARD O., Boise. Died 31, 1992, aged 75. Graduate of University of Illinois, 1945. Licensed in Idaho in 1956. Dr Vycital was a member of the Ada County Medical Society.

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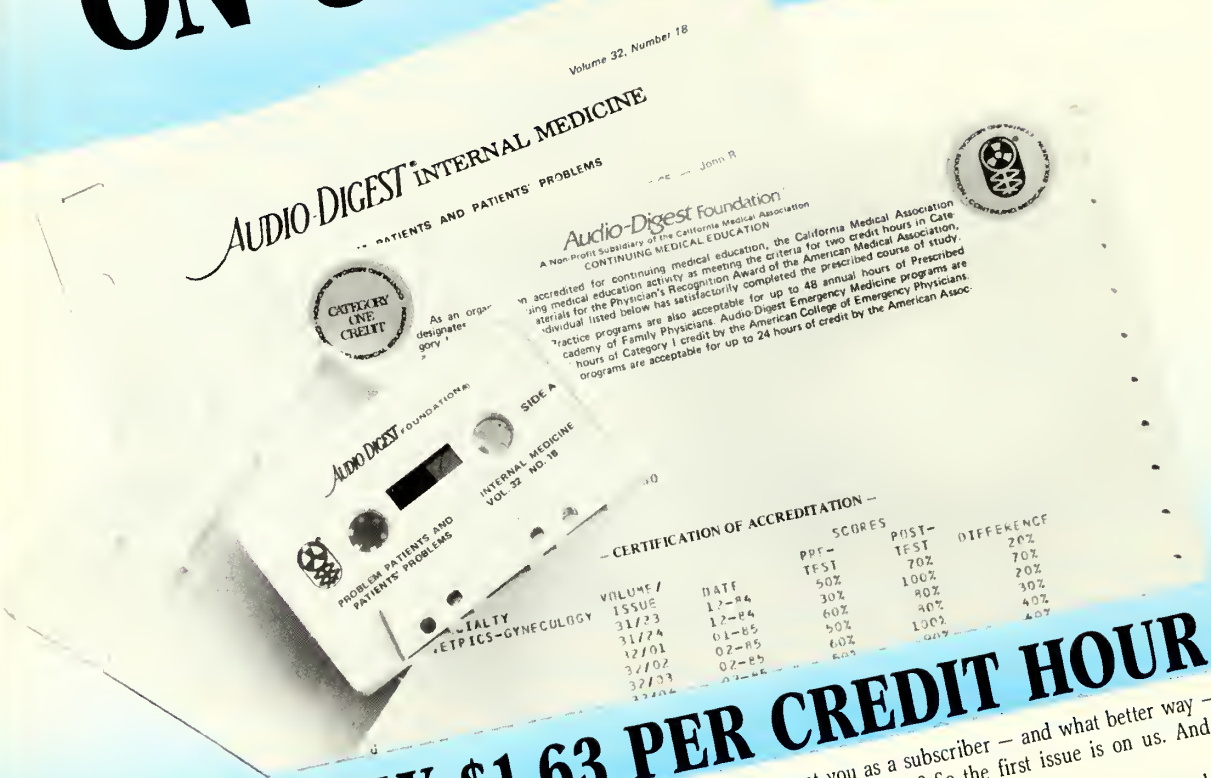

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Articles

Neurosurgical Management of the Acquired Immunodeficiency Syndrome
An Update

BRIAN T. ANDREWS, MD, *and* THOMAS P. KENEFICK, MD, *San Francisco, California*

A retrospective review of a 24-month experience on the neurosurgical service at a large metropolitan hospital identified 33 patients with the acquired immunodeficiency syndrome (AIDS) who underwent diagnostic or therapeutic procedures. Intracranial mass lesions unresponsive to empiric medical therapy for presumed *Toxoplasma gondii* encephalitis underwent diagnostic biopsy in 22 patients: primary lymphoma was identified in 10 (45%) of these patients, and biopsy led to a treatable diagnosis in 16 of the 22. Patients with lymphoma were significantly more likely to have a single mass lesion than those with other diagnoses. The remaining 11 patients had a wide variety of neurologic disorders, including multiple strokes and transverse myelitis, aspergillous fungal infection of the base of the skull, primary lymphoma of the spinal cord, cat-scratch fever of the spine causing painful radiculopathy, hydrocephalus associated with cryptococcal meningitis, and progressive inflammatory peripheral neuropathy. Two patients had lymphoma within the subarachnoid space. Three patients with well-controlled AIDS underwent elective neurosurgical therapy for intractable radiculopathies due to herniated lumbar discs in 2 and cervical spondylosis in 1.

Current treatment strategies in AIDS appear to have limited the need for brain biopsy, but the spectrum of neurologic disorders has broadened, requiring continued participation by neurologists and neurosurgeons. With improved long-term survival, the elective treatment of non-AIDS-related neurologic disorders in selected patients may be appropriate.

(Andrews BT, Kenefick TP: Neurosurgical management of the acquired immunodeficiency syndrome—An update. West J Med 1993 Mar; 158:249-253)

In the first decade of the acquired immunodeficiency syndrome (AIDS) epidemic, it was quickly realized that patients infected with the human immunodeficiency virus (HIV) who progressed to AIDS had a high incidence of widely varied neurologic disease involving both the central and peripheral nervous system.[1-4] Although diagnostic biopsies were used frequently in the discovery and initial treatment of many of these disorders, a rational attempt was made to limit the need for invasive procedures by empiric medical treatment of the most common disorders. Specifically, because of the high incidence of *Toxoplasma gondii* infection among patients with intracranial mass lesions, the treatment of this disorder without biopsy was recommended, limiting biopsy to those patients whose lesions failed to respond.[1,5,6] Persistence of the AIDS epidemic has continued to widen the spectrum of diseases that require both diagnosis and treatment by neurologists and neurosurgeons. Also, as the medical therapy for AIDS has led to more patients surviving long term with a higher quality of life,[7-9] the treatment of other non-AIDS-related neurologic disorders has become appropriate in selected circumstances. To further elucidate the breadth of conditions affecting patients with AIDS that required the assistance of the neurosurgery service, we reviewed a 24-month experience at a large metropolitan San Francisco, California, hospital.

Patients and Methods

We did a retrospective medical records review of all patients treated through the neurosurgical service at the California Pacific Medical Center, a large metropolitan teaching hospital in San Francisco, between August 1, 1989, and August 1, 1991. All neurosurgical consultations, procedures, and clinical follow-up examinations were done by us; follow-up was carried out by direct or telephone interview with the patients, their caretakers, or their primary care physicians and was completed by November 1991.

Patients with intracranial mass lesions were generally evaluated for antibodies to *T gondii* and, if seropositive, treated empirically using appropriate antibiotics for presumed *T gondii* encephalitis for two to four weeks before neurosurgical referral. Those seronegative for *T gondii* antibodies or who did not show a clinical or radiographic response to treatment were referred to the neurosurgical service for tissue biopsy.

Results

A total of 33 patients with a known diagnosis of AIDS underwent neurosurgical evaluation and intervention (Table 1). Intracranial mass lesions either unresponsive to empiric medical therapy for *T gondii* encephalitis or seronegative for antibodies to *T gondii* required diagnostic biopsy in 22 patients: primary lymphoma was identified in 10. In 9 of the 10 patients the lymphoma was noted as a single mass lesion by computed tomography (CT) or magnetic resonance imaging (MRI). Progressive multifocal leukoencephalopathy and *T gondii* encephalitis were noted in 4 patients each. Three of the four with leukoencephalopathy and all of those with *T gondii* encephalitis had multiple lesions as seen by CT or

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CNS = central nervous system
CSF = cerebrospinal fluid
CT = computed tomography
HIV = human immunodeficiency virus
MRI = magnetic resonance imaging

TABLE 1.—*Neurosurgical Procedures Done in 33 Patients With the Acquired Immunodeficiency Syndrome*

Procedure		*Patients, No.*
Brain biopsy for intracranial mass lesion		22
Lymphoma	10	
Progressive multifocal leukoencephalopathy	4	
Toxoplosmo gondii encephalitis	4	
Cryptococcal brain abscess	1	
Metastatic adenocarcinoma of lung	1	
Nondiagnostic	2	
Brain and meningeal biopsy for multiple strokes and transverse myelitis		1
Transsphenoidal resection of aspergillosis		1
Biopsy of spinal cord tumor (lymphoma)		1
Excision of lumbar facet mass (cat-scratch disease)		1
Lumboperitoneal shunt (cryptococcal meningitis)		1
Ommaya reservoir (lymphomatous meningitis)		2
Peripheral nerve biopsy		1
Elective spinal procedures		3
Lumbar disc disease with radiculopathy	2	
Cervical disc disease with radiculopathy	1	

MRI. One patient each had single lesions found to be *Cryptococcus neoformans* abscess and metastatic lung cancer. Single lesions were thus most often lymphoma, and multiple lesions were more often *T gondii* or progressive multifocal leukoencephalopathy (χ^2, 1 *df*, $P < .05$). Two patients (9%) had abnormal but nondiagnostic tissue. There were no complications of intracranial biopsy in this series, and biopsy led to the diagnosis and subsequent treatment of specific neurologic disorders in 16 of the 22 patients (73%).

One patient had the abrupt development of a thoracic-level transverse myelitis, followed by two sequential strokes in the right hemisphere. Magnetic resonance imaging of the spinal cord showed no abnormalities, and MRI of the brain suggested infarction in the distribution of the middle cerebral artery. Echocardiography revealed no abnormalities, and cerebral angiography showed no evidence of vascular occlusions or vasculitis. Serologic and cerebrospinal fluid (CSF) studies for neurosyphilis were negative. Finally, diagnostic brain, cerebrovascular, and meningeal biopsies were done but showed only normal tissues. The patient was treated with a course of prednisone for presumed vasculitis, without further clinical deterioration.

One patient with progressive unilateral vision loss and a destructive process involving the frontal base of the skull, sphenoid sinuses, and medial orbit (Figure 1) underwent transsphenoidal debridement of an inflammatory mass that proved to be infection with *Aspergillus fumigatus;* despite subsequent antibiotic therapy, progressive unilateral blindness, ophthalmoplegia, and facial numbness developed before the disease process stabilized.

A single patient with a progressive T-6–level myelopathy had a tumor within the thoracic spinal cord; biopsy identified a primary lymphoma, leading to treatment with irradiation. Another patient with a painful L-5 motor and sensory radiculopathy had a destructive lesion involving the right L5-S1 lumbar facet process (Figure 2). Surgical decompression of this lesion resulted in an immediate lessening of symptoms and signs of nerve root compression, and special staining of the excised tissue identified the organisms associated with cat-scratch fever. Subsequent antibiotic therapy with erythromycin was administered.

One patient required a lumboperitoneal shunt for hydrocephalus after the successful treatment of cryptococcal meningitis, and two required placement of an Ommaya reser-

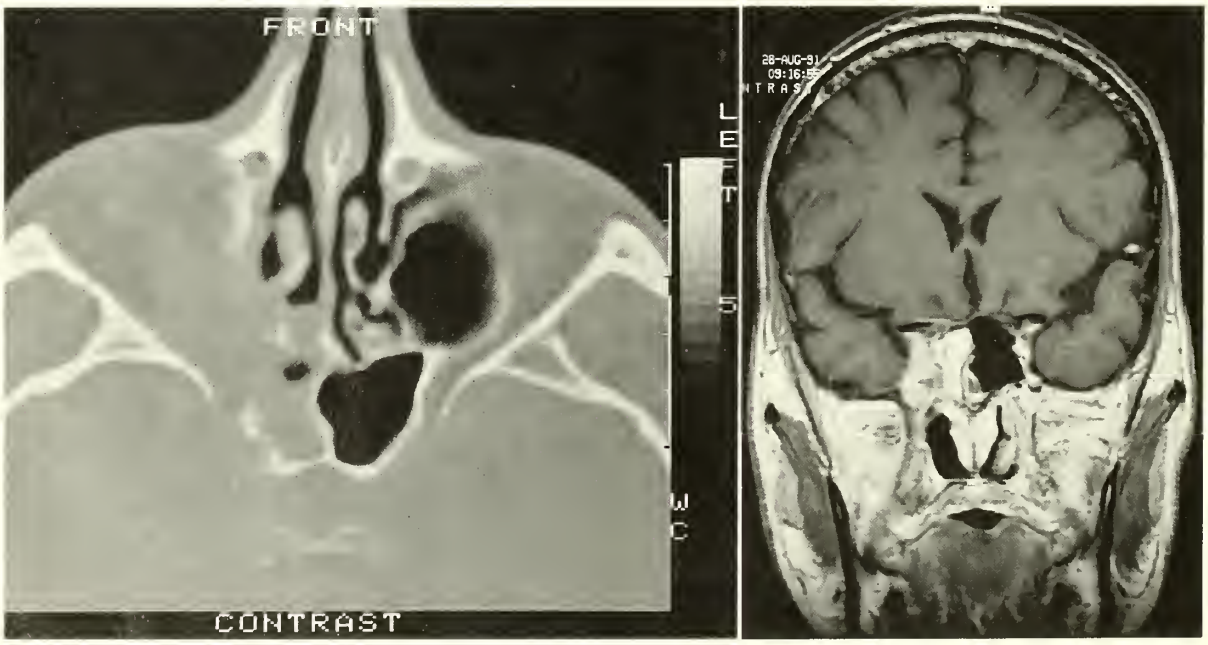

Figure 1.—Left, A computed tomographic scan with bone window settings and, **right,** a T1-weighted axial and coronal magnetic resonance image shows a destructive mass involving the sphenoid and ethmoid sinuses and medial orbit in a patient with progressive ipsilateral loss of vision. Transsphenoidal debridement proved this to be caused by infection with *Aspergillus fumigotus.*

voir for the chemotherapeutic treatment of lymphomatous meningitis. A single patient with a progressive diffuse axonal neuropathy required a diagnostic sural nerve biopsy, which showed a mononuclear inflammatory neuropathy.

Three patients with well-controlled AIDS underwent elective surgical procedures for intractable radiculopathies due to herniated lumbar discs in two and cervical spondylosis in one, with satisfactory treatment results in each.

Clinical follow-up showed that among the 16 patients

Figure 2.—A T1-weighted magnetic resonance image of the lumbar spine in a patient with progressive L-5 radiculopathy shows a destructive mass involving the right-sided facet process **(arrowhead)** that at the time of surgical excision proved to be the result of localized infection with the bacillus responsible for cat-scratch fever.

with intracranial mass lesions given subsequent treatment, a meaningful beneficial response was noted in 12. Four patients with central nervous system (CNS) lymphoma (3 in the brain and 1 in the spinal cord) died within one to four months of biopsy despite radiation therapy, whereas the patients with other forms of brain disorders all continue to survive from 4 to 20 months later. The patients with aspergillosis of the base of the skull and spinal cat-scratch fever continue to do well 12 months later. The patient with a lumboperitoneal shunt for cryptococcal meningitis required shunt revision after three months but has since done well for 18 months. Both patients with Ommaya reservoirs in place had a clinical response to intrathecal chemotherapy and continued to survive at the time of follow-up four and seven months later. The three patients with cervical or lumbar radiculopathy due to disc disease are each doing well with no further neurologic symptoms.

Discussion

Initial experience with patients harboring AIDS-related intracranial mass lesions showed that most of the lesions were caused by infection with *T gondii*[1,3-6] and that an initial period of antibiotic therapy for this organism would effectively treat and therefore presumptively diagnose the infection without the need for tissue biopsy.[1,5,6] It was recommended that patients with progressive clinical deterioration or enlargement of the lesions on repeated MRI despite three or more weeks of antibiotic therapy undergo biopsy for definitive diagnosis.[1,5,6] More recently Ciricillo and Rosenblum reported that single intracranial mass lesions visualized by MRI are most often lymphoma and argued for early biopsy in such cases to facilitate early treatment with irradiation.[10,11] Our results would appear to support this finding; 9 of 12 patients with single lesions harbored lymphoma, whereas 7 of 8 patients with *T gondii* or progressive multifocal leukoencephalopathy had multiple lesions by CT or MRI. Unless a patient is rapidly deteriorating from the mass lesion, however, we still recommend an initial period of empiric therapy for *T gondii*. We did an assay of serum antitoxoplasma antibody in all patients with intracranial mass lesions: patients with a negative IgG titer are unlikely to have *T gondii* encephalitis,[1,3] and such patients are considered for early biopsy and definitive diagnosis.

Excluding those patients who test negative for antibodies to *T gondii*, empiric antibiotic therapy for most patients with intracranial mass lesions for *T gondii* encephalitis appears to be reasonably effective in distinguishing patients with this infection from those considered for intracranial biopsy; however, 4 of 22 patients who underwent biopsy proved to have *T gondii* infection that had progressed clinically or on x-ray films despite antibiotic therapy. We are unaware, however, of the total number of patients successfully treated for *T gondii* encephalitis at our institution and never brought to our attention for biopsy consideration.

Patients with multiple intracranial lesions that are subcortical with little or no mass effect, contrast enhancement, or edema by CT or MRI (Figure 3) most often have progressive multifocal leukoencephalopathy.[1,3,12-14] Such patients are usually offered a course of presumptive treatment of *T gondii* encephalitis, but in general we avoid doing a biopsy unless repeated MRI shows the development of a mass effect. Despite this cautionary stance, four patients in this series who underwent biopsy for mass lesions had the encephalopathy.

In our study, the biopsy of intracranial mass lesions identified a variety of lesions, including lymphoma, metastatic tumors, fungal and parasitic infections, and progressive multifocal leukoencephalopathy. Of the 22 patients who underwent biopsy, 16 (73%) had diseases that were amenable to subsequent specific therapy. This indicates that biopsy remains extremely worthwhile. Recent reports suggest that radiation therapy for primary AIDS-related CNS lymphoma results in improvement or stabilization of disease in 85% of cases.[11,15] Our results would not seem to support the practice of treating those patients in whom empiric antitoxoplasmotic therapy fails with empiric radiation therapy for CNS lymphoma. Overall, only 10 of the 22 patients undergoing biopsy in this series had lymphoma, and such a practice would lead to inappropriate radiation therapy in a considerable number of patients. Other recent series also highlight the breadth of diagnoses found at the time of biopsy: Levy and co-workers reported that among 50 neurologically symptomatic patients with AIDS undergoing biopsy, only 14 had lymphoma, and only 2 others had lesions possibly responsive to radiation therapy.[16] Similar to the results in our series, however, biopsy led to additional therapy for specific infectious or neoplastic disorders in two thirds of the patients, suggesting that it is worthwhile in guiding subsequent therapy.

One patient with a progressive thoracic-level paraplegia subsequently had two strokes involving the middle cerebral artery distribution. Cardioembolic stroke was thought to be ruled out by normal echocardiography; despite negative cerebral angiography and normal findings on meningeal, brain, and vessel biopsies, the patient was treated with a course of steroids for presumed vasculitis, and his condition stabilized.

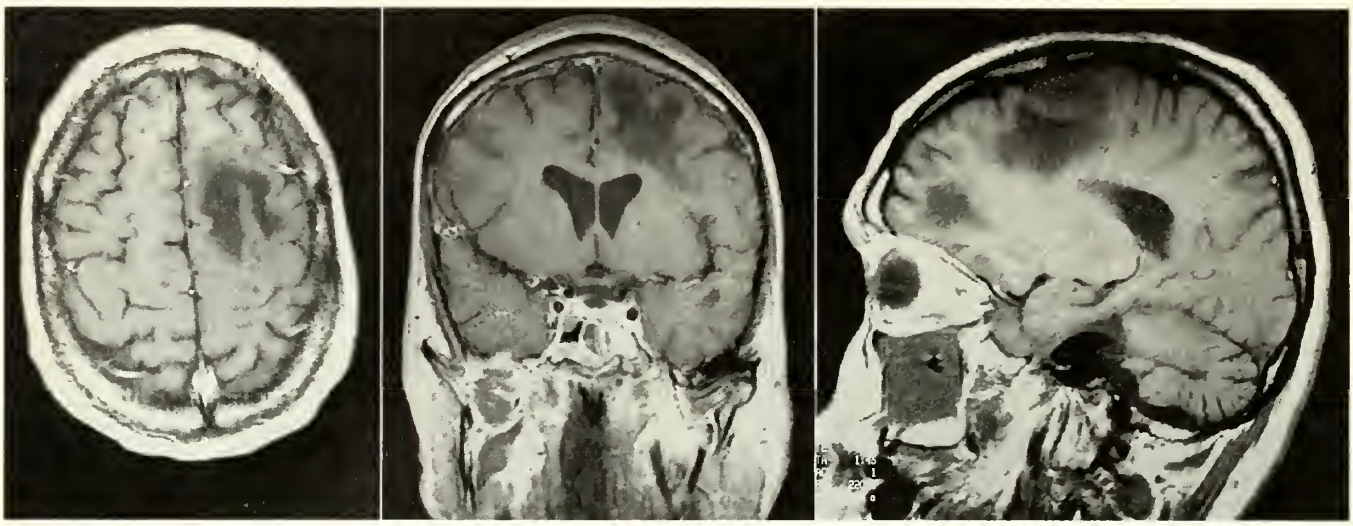

Figure 3.—Left, Axial, **center,** coronal, and, **right,** sagittal T1-weighted magnetic resonance images (MRI) in a patient with progressive focal neurologic deficits. This MRI appearance is most compatible with progressive multifocal leukoencephalopathy, and this patient did not undergo biopsy.

Progressive myelopathy has been described in patients with AIDS, which on pathologic examination shows vacuolar changes similar to that of subacute combined degeneration.[1,17] Vacuolar myelopathy may coexist with AIDS dementia complex,[17] but an association of myelopathy with hemispheric strokes has not previously been recognized. Other causes of myelopathy may include spinal cord compression from epidural lymphoma, infectious myelitis from cytomegalovirus or herpesvirus, or tuberculous abscess.[1,4] Cerebral infarction associated with AIDS has been previously reported, as a result of nonbacterial thrombotic endocarditis,[3,18] meningovascular syphilis,[4] and herpes zoster arteritis.[15] None of these diagnoses appeared to be present in our patient with repeated strokes, and the cause of infarction remains unknown.

Opportunistic fungal infections are common in patients with AIDS[1,3,4,6] and in our series included infection involving the CSF, brain, and base of the skull. A single patient required placement of a shunt for communicating hydrocephalus despite effective treatment of cryptococcal meningitis. Communicating hydrocephalus is a known but unusual complication of cryptococcal meningitis[19] and may persist despite adequate and ongoing treatment of the infection, requiring either serial lumbar punctures or a shunt for resolution. Before placement of a shunt is considered, the adequacy of the treatment of meningitis must be assessed with repeated analysis of the CSF, including india ink stains, fungal cultures, and cryptococcal antigen titers. Relapse may occur despite intensive therapy[20] and result in similar symptoms suggesting increased intracranial and CSF pressure. Should these tests for active infection remain negative, repeated lumbar punctures or a shunt should be considered, even if the ventricle has not enlarged. Rarer but also well described is the occurrence of fungal intracranial mass lesions with *C neoformans,* so-called cryptococcomas[21]; a single patient in our series had such a lesion and has had a clinical response to antifungal therapy using amphotericin B and flucytosine. Although sinusitis is a frequent complication of AIDS, it usually results from bacterial infection.[22] Fungal sinusitis with a variety of organisms has been described, but invasion into the base of the skull and orbit, as occurred from aspergillosis in one patient in our series, is rare.

Among the more unusual opportunistic infections in patients with AIDS is the systemic occurrence of cat-scratch fever. The small gram-negative bacterium associated with cat-scratch fever usually causes lesions in the skin and lymph nodes and rarely the liver and bone.[20] We had one patient with an expansile and destructive lesion involving a lumbar facet joint resulting in compressive radiculopathy; specimens of the lesion stained for this organism. The lesion responded well to surgical decompression followed by antibiotic therapy with erythromycin.

The medical treatment of AIDS, particularly the use of zidovudine prophylaxis,[8,9] has led to more patients with AIDS achieving long-term survival with an overall higher quality of life. Currently the average survival for patients after the diagnosis of AIDS is 15 months,[3] and a substantial number of patients survive many years with an acceptable level of function and quality of life. This brings into consideration the treatment of non–AIDS-related but disabling conditions. In our series, three patients, each with well-controlled AIDS and an otherwise high level of function, were treated for painful radiculopathies that had been refractory to conservative measures. In each case surgical treatment was considered elective, and each patient had a successful result with no untoward complications.

Conclusions

Persistence of the AIDS epidemic has resulted in an increasing breadth of conditions facing neurologists and neurosurgeons involved in the care of patients with AIDS. Such disorders include not only intracranial mass lesions but also those of the spinal cord, nerve roots, peripheral nerves, and CSF. Diagnostic biopsy of intracranial mass lesions in patients with negative antitoxoplasma serologic tests or having a lack of response to the treatment of toxoplasmosis appears to be useful in guiding subsequent treatment. The neurosurgical treatment of non–AIDS-related disorders in those AIDS patients who are otherwise doing well appears to be worthwhile.

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* * *

SITTING IN MEDICAL GRAND ROUNDS THINKING ABOUT MY DIVORCE

Dr Chatterjee is saying
that the heart can harm
itself, can make the wrong choices
and fail. It has to do
with receptors, landing sites
along the wall of the cell
where hormones bring
their meticulous shapes
like messages of rescue.
But as the heart begins to fail,
he says, the receptors
deactivate—
as if to turn their faces
to the wall.
And the failing heart fails more.

I wondered if the mind
could work that way,
choosing the wrong response,
like stepping into a mudslide,
like what happens when love fails
and we harm the ones we love.

DAVID WATTS, MD©
San Francisco, California

Articles

Ocular Examination and Diagnosis in Patients With the Acquired Immunodeficiency Syndrome

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Ocular involvement is seen frequently and is an important source of morbidity in patients with the acquired immunodeficiency syndrome. We outline here the general skills of physical diagnosis valuable to primary care physicians or infectious diseases specialists in recognizing and evaluating ocular complaints in patients infected with the human immunodeficiency virus. We provide an overview of common ocular diseases in these patients, with an emphasis on signs and symptoms that aid in the differential diagnosis.

(Gariano RF, Rickman LS, Freeman WR: Ocular examination and diagnosis in patients with the acquired immunodeficiency syndrome. West J Med 1993 Mar; 158:254-262)

Ocular involvement occurs in as many as 70% of patients with the acquired immunodeficiency syndrome (AIDS) and may herald numerous systemic infections.[1] Indeed, ocular symptoms are on occasion the presenting manifestations of human immunodeficiency virus (HIV) infection. We describe ocular examination findings and the differential diagnosis of patients infected with HIV, with an emphasis on physical diagnosis and treatment options. It is hoped that this review of ocular examination techniques and the overview of diagnostic possibilities will facilitate the diagnosis, referral, and treatment of patients with AIDS.

History and Physical Examination

If the chief complaint of a patient with AIDS relates to vision, the physician should ascertain whether one or both eyes are involved and should inquire whether vision loss is acute or chronic, if it occurred suddenly or gradually, and whether it is worsening or resolving. The nature of the visual change—blurring, diplopia, field defects, photopsia, or new floaters—is all important. Generally, a loss of acuity occurs if the ocular media—cornea, lens, anterior and vitreous chambers—are hazy or there is disease of the macula and optic nerve; floaters are typical of posterior uveitis, photophobia is a common sign of iritis, and visual field defects may denote peripheral retinal or central nervous system disease.

Visual acuity is the single most important piece of information required in evaluating patients. Because visual changes such as floaters, photopsia, and field defects may not be associated with changes in acuity, and because of the emotional effects of visual symptoms, the patient's subjective description of vision loss is never adequate, and only exceptionally does it correlate with objective findings. For medicolegal reasons as well, before intervention, the primary care physician must assess and quantify visual acuity for all patients with visual symptoms. If formal acuity measurement by the Snellen chart is unavailable or beyond the patient's capability, less quantitative assessments such as "counts fingers" or "no light perception" are valuable.

The testing of peripheral vision by confrontation may detect sizable field cuts such as seen in hemianopias or extensive retinal detachments, but it is unlikely to detect scotomas or smaller deficits. In these cases, formal visual field testing can be done if needed for diagnosis or for monitoring therapy.

The pupillary examination is informative in that reactivity to light depends on the number of retinal elements recruited by the stimulus. Therefore, changes in pupillary reactions indicate functional compromise of a substantial percentage of the retina or optic nerve. The most important maneuver in the pupillary examination is the detection of an afferent pupillary defect, also known as the Marcus Gunn pupil. An afferent pupillary defect generally occurs in disease of the optic nerve or with widespread retinal damage.

Generally, ocular motility problems cause symptoms of double vision and, in patients with AIDS, may reflect central nervous system disease involving the brain stem, usually a basilar meningitis, or orbital tumors that restrict the action of the extraocular muscles. Subtle displacements of the globe are indicated by asymmetry of the corneal light reflections.

Lymphatics for the external ocular structures including the lids, conjunctivae, and cornea drain into the ipsilateral preauricular and submandibular nodes. Preauricular adenopathy is an important sign of chlamydial, herpetic, adenoviral, or gonococcal keratoconjunctivitis, but may be misleading in patients with AIDS if there is diffuse lymphadenopathy. There are no lymphatic structures within the eye itself, so that intraocular infections do not produce adenopathy.

The slit lamp allows the various layers of the eye to be seen in cross-section. This instrument is generally easily accessible only to ophthalmologists. A corneal examination may reveal infectious infiltrates or inflammatory cell precipitates on the endothelium. The anterior chamber can be scrutinized for the presence of cells and protein, specifically inflammatory cells such as polymorphonuclear leukocytes, macrophages, and lymphocytes as well as fibrin and immunoglobulins, an indication of intraocular inflammation. Sim-

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ABBREVIATIONS USED IN TEXT

AIDS = acquired immunodeficiency syndrome
CMV = cytomegalovirus
HIV = human immunodeficiency virus

ilarly, the slit-lamp beam can be focused in the anterior vitreous cavity where the presence of leukocytes may indicate infection in the posterior segment, whereas pigmented cells may reflect retinal tears, detachments, or hemorrhages.

The hand-held direct ophthalmoscope provides a limited view of the posterior fundus. In most patients, only the optic nerve and macula can be seen. Ophthalmologists generally use an indirect ophthalmoscope to examine the retina and optic nerve. This technique provides stereopsis, wide-angle viewing (Figure 1), the ability to visualize peripheral retina, and the option of using a powerful light source to see the fundus when the ocular media are unclear. Because of these advantages, a clinically suspicious diagnosis or symptom should never be dismissed solely on the basis of a negative examination with the hand-held direct ophthalmoscope, particularly if the examination is done on an undilated eye. Pupillary dilation greatly eases visualization of the retina and enables a much larger retinal area to be inspected (Figure 1) when doing either direct or indirect ophthalmoscopy.

Ocular Manifestations of the Acquired Immunodeficiency Syndrome

Ocular manifestations of AIDS can be grouped into four main categories[2]: benign AIDS retinopathy or microangiopathy, opportunistic and other retinal-choroidal infections, neuro-ophthalmic lesions, and neoplasia.

Retinopathy Related to Human Immunodeficiency Virus

Retinopathy related to HIV, or microangiopathy, is found in 30% to 60% of infected patients[1-4] and may precede the occurrence of major AIDS-related infections. On funduscopic examination, small fluffy yellow-white lesions called cotton-wool spots are most often found in the posterior pole (Figure 2). These are located in the most anterior layers of the retina (the nerve fiber layer) and represent microinfarcts, caused by precapillary arteriolar occlusion, of nerve bundles coursing toward the optic nerve head. Small "dot and blot" intraretinal hemorrhages are also frequently found. Retinopathy related to HIV presumably occurs because of a microangiopathy and in appearance is similar to findings in diabetes mellitus, hypertension, and some vasculitic and rheologic disorders.

Evidence for a microangiopathy can be detected in the anterior segment of the retina of nearly all patients with AIDS. On slit-lamp examination, conjunctival vessels generally show an irregular caliber, fragmentation, microaneurysms, and sludging of blood flow similar to that seen in some patients with sickle cell disease. Although the cause of microangiopathy in AIDS is unclear, it seems to be related to the degree of immune suppression because it is seen relatively less frequently in HIV-infected persons who have not yet had major infections and is inversely related to the ratio of $CD4^+$ (helper) to $CD8^+$ (suppressor) T lymphocytes.[3] Patients with cotton-wool spots have greater weight loss, lower leukocyte counts, and a higher risk of impending infection than those without these retinal findings.[4]

Retinal microangiopathy is nonprogressive and nearly always asymptomatic[5]; its diagnostic significance lies mainly in that cotton-wool spots in the presence of dot-blot hemorrhage may mimic viral retinitis. As a rule, the spots are asymptomatic, smaller than a disc diameter, clustered in the posterior pole, and disappear over several weeks, whereas foci of cytomegalovirus or other serious retinal infections cause visual symptoms, can be much larger, may be found in any region of the retina, and do not spontaneously resolve (discussed later). Because cotton-wool spots appear at some time in the retina of most patients with AIDS, it is important that internists, infectious diseases specialists, and primary care providers become familiar with the appearance of these benign lesions.

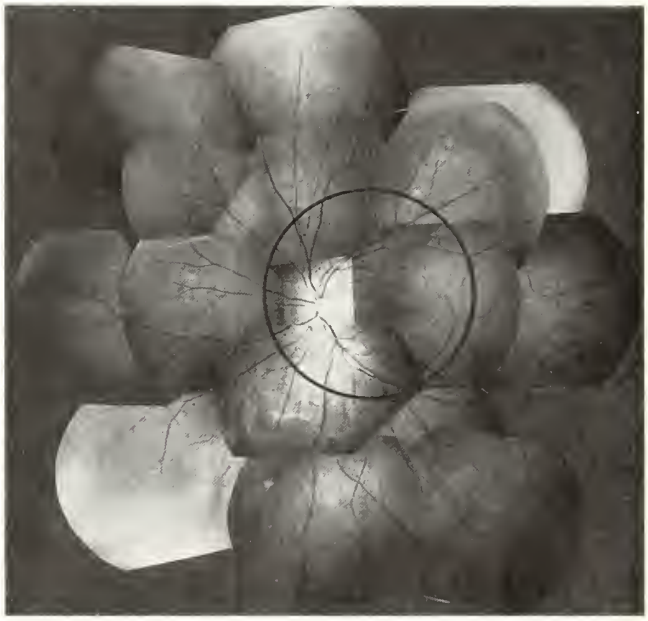

Figure 1.—The photomontage shows the retinal surface extending from the macula posteriorly to the ora serrata anteriorly. The direct ophthalmoscope gives a monocular view slightly larger than the diameter of the optic disc (1.5 mm). Indirect ophthalmoscopy with a 20-diopter lens illuminates a much larger area of retina **(circled region).** When combined with the technique of scleral depression, the indirect ophthalmoscope allows stereoscopic visualization of the entire retina.

Figure 2.—The fundus of a 36-year-old man with the acquired immunodeficiency syndrome reveals scattered cotton-wool spots typical of human immunodeficiency virus (HIV) retinopathy or microangiopathy. The lesions obscure retinal vessels because of their superficial location. Small blot hemorrhages are frequently seen in HIV retinopathy as well.

Figure 3.—A cytomegaloviral retinitis lesion involves the superior optic nerve border and threatens the fovea. Lesions located at or near the fovea or optic nerve require evaluation within days, as complete loss of vision may ensue within 1 to 2 weeks.

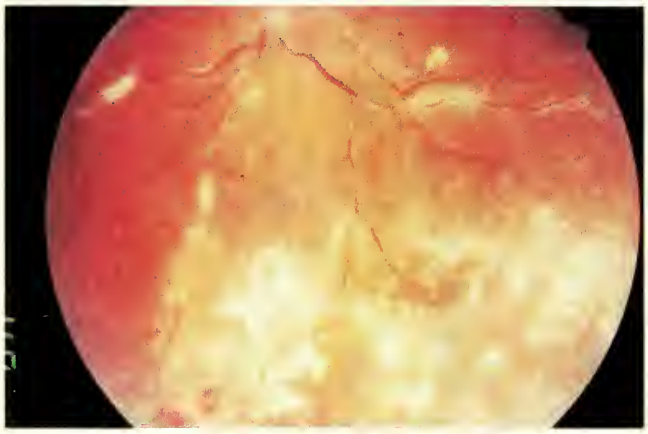

Figure 4.—Early in the course of cytomegaloviral retinitis, the retinal lesion appears white and granular and is often associated with hemorrhage. Note the vascular sheathing above this inferior peripheral lesion. Left untreated, this lesion would likely progress over several weeks to involve the macula.

Cytomegalovirus

Cytomegalovirus (CMV) is a common pathogen that usually causes asymptomatic infection in noncompromised hosts. More than 90% of patients with AIDS have evidence of recent or reactivated CMV systemic infection, and about a third of these experience severe manifestations, usually from pneumonitis, esophagitis, gastritis, hepatitis, colitis, encephalitis, and retinitis.[6]

Cytomegalovirus retinitis occurs in 15% to 40% of patients with AIDS[1,2,7,8] and, in contrast to the noninfectious ocular lesions of AIDS, demands aggressive intervention to prevent severe loss of vision.[9,10] Human CMV invades retinal cells and causes necrosis of all retinal layers. The inflammatory response to this virus in the retina is minimal, and ocular pain, redness, discharge, or intense photophobia suggest a different diagnosis; CMV retinitis is essentially painless. In nearly 95% of cases, the blood cultures are positive for the virus.[11] Because CMV viremia is present in more than 50% of AIDS patients,[12] however, the diagnosis is based entirely on the characteristic appearance of the retinal lesions. Early lesions appear as granular white patches of retinal edema,

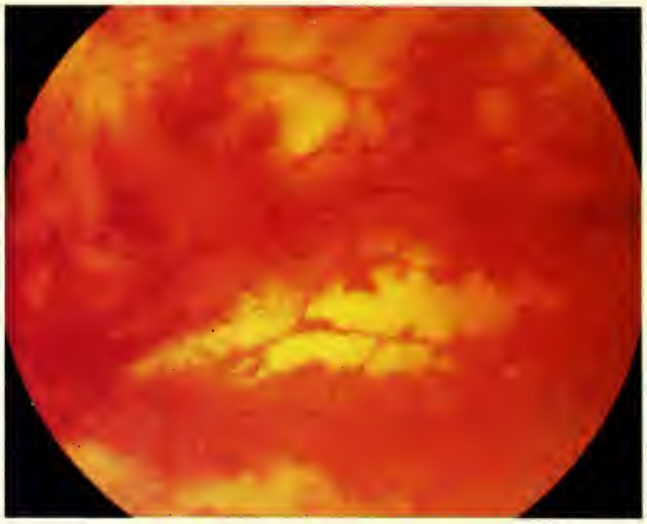

Figure 5.—The fundus photograph is taken of a patient with acute retinal necrosis. All retinal changes occurred over a 3-week period. Note the paravascular sparing and involvement of deep retinal layers—that is, beneath the retinal vessels. The peripheral retina shows small areas of whitening. These features may help to distinguish this disorder from cytomegaloviral retinitis.

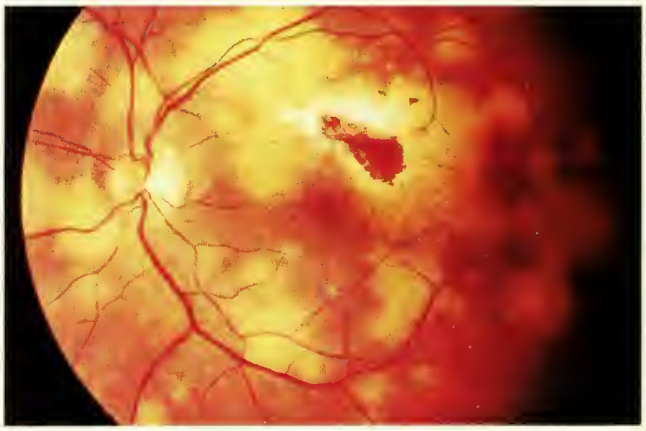

Figure 6.—The fundus photograph is taken of a patient with two ocular opportunistic infections. The superficial white hemorrhagic lesion near the fovea is active cytomegaloviral retinitis. Pale orange fluffy lesions located in the deeper choroidal layers (behind retinal vessels) contain *Pneumocystis carinii* organisms. These latter lesions do not affect vision.

Figure 7.—The fundus photograph of a patient with the acquired immunodeficiency syndrome shows both cytomegaloviral retinitis and benign human immunodeficiency virus retinopathy. The infectious focus, located temporal to the fovea, is distinguished from the hemorrhage and circumpapillary cotton-wool spots caused by a microangiopathy, as described in the text.

often accompanied by hemorrhage (this has been likened to "cottage cheese and catsup" [Figures 3 and 4]). Often a vasculitis is present, and atrophic retina may be seen in areas affected earlier on in the course. Late in the disease, the optic nerve becomes pale owing to the extensive loss of retinal cells and axonal degeneration.

Infection may begin in the posterior pole or in the midperiphery and spreads as an advancing border, leaving an atrophic retina behind. The symptoms depend on the site of infection. If the active lesion is near the fovea or optic nerve, the patient has blurred vision. If only peripheral retina is involved, the patient may be asymptomatic or notice visual field defects or, commonly, floaters. An important feature of the disease is its relatively slow progression; measurable changes in the appearance of the lesion and symptomatic deterioration usually occur over at least one to two or more weeks. Infrequently, however, retinal detachment occurs, and extensive vision loss may ensue quickly. About two thirds of patients present with unilateral involvement, but the natural course of the disease without treatment is a progression to blindness in both eyes of all patients.

Posterior lesions, shown in Figure 3, encroach on the fovea and optic nerve and are likely within a period of several weeks to be associated with a pericentral scotoma and visual blurring. In contrast, a lesion located in the midperiphery (Figure 4) may produce less bothersome floaters or be entirely asymptomatic. A peripheral lesion may spread centrally, however; in this case, serial fundal photographs are used to document the advancing border of retinitis, leaving in its wake atrophic nonfunctional retina.

The differential diagnosis of CMV retinitis includes several fungal, parasitic, and other infections, including candidal, toxoplasmal, syphilitic, *Mycobacterium avium-intracellulare,* and *Histoplasma capsulatum* chorioretinitis. These disorders occur much less frequently than CMV retinitis, and not all are clinically important or even clinically apparent.[1,2,7,13-19] Conditions such as toxoplasmal and candidal retinitis are relatively rare in these patients despite the frequent occurrence of systemic or mucosal infection with these organisms.[1,19,20] They can be further distinguished from CMV retinitis by the typical accompanying dense vitritis that makes the ophthalmoscopic view hazy.[1,20] Disseminated tuberculosis may appear as a multifocal choroiditis but most often presents as an iritis, with photophobia the major symptom.[1,2] These other diagnoses are often greatly facilitated by specific laboratory tests.

Acute retinal necrosis is a more fulminant retinitis caused by herpes simplex virus or varicella zoster virus, is much less common in AIDS patients, and usually is more rapid in onset and progression.[1,13,16] Acute retinal necrosis may appear similar to CMV retinitis, with well-demarcated, confluent, deep retinal lesions associated with minimal hemorrhage; subtle features such as the presence of substantial intraocular inflammation (uveitis), retinal paravascular sparing, and peripheral retinal whitening favor this diagnosis (Figure 5).[13,16,21] The distinction is an important one, because acute retinal necrosis may be treated with acyclovir, thereby avoiding possible serious complications of anti-CMV therapy (discussed later). Cases of unilateral acute retinal necrosis progress to contralateral involvement in about 50% of patients, and retinal atrophy with subsequent detachment occurs commonly.

Choroidal *Pneumocystis carinii* infection has become more common with the increased use of prophylactic aerosolized pentamidine, although the actual incidence is unknown. These lesions characteristically appear as pale cream or orange space-occupying lesions beneath the retinal vessels (in the choroid, the vascular coat beneath the retina), are unilateral or bilateral, and rarely are symptomatic or reduce vision.[17,18] Other causes of opportunistic choroiditis in patients with AIDS are *Cryptococcus neoformans, Mycobacterium kansasii, Histoplasma capsulatum,* and *Candida* species.[19] Figure 6 shows a patient with both CMV and *P carinii* ocular disease; the lesions are easily differentiated

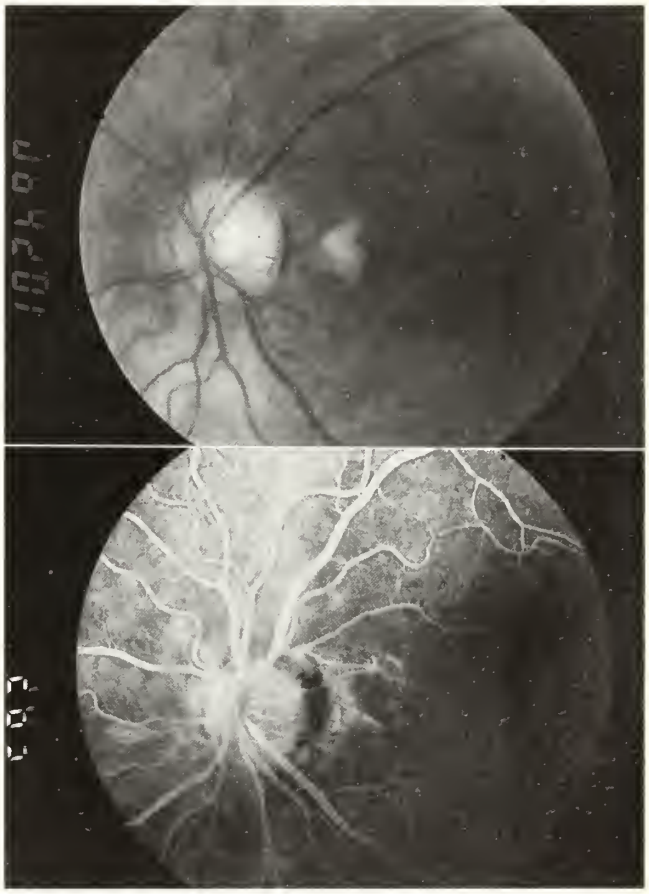

Figure 8.—Top, The patient has a small fluffy white lesion located between the fovea and optic disc. It may be difficult clinically to distinguish a cotton-wool spot from a cytomegaloviral focus of this size. **Bottom,** A fluorescein angiogram of the same lesion shows blockage of underlying choroidal fluorescence, typical of cotton-wool spots, without significant leakage of dye from the site, suggesting it is not an infectious or inflammatory lesion.

by appearance and location (superficial retinal CMV lesion versus deeper choroidal *P carinii* infection). Several reports indicate regression of the choroidal lesions following the intravenous administration of pentamidine or of trimethoprim and sulfamethoxazole (Septra),[22] yet indications for the specific treatment of asymptomatic *P carinii* choroidopathy remain uncertain. Though the diagnosis of disseminated *P carinii* infection may be suggested by the characteristic appearance of choroidopathy, and isolated ocular disease may rarely be the earliest clinical manifestation of disseminated *P carinii,* it is unclear from the literature whether early treatment with systemic therapy would alter the course of disease.[23,24]

The edema and hemorrhage of CMV retinitis may at times be difficult to differentiate from the cotton-wool spots

and small hemorrhages of HIV-related microangiopathy, especially since both conditions are relatively common. Cotton-wool spots are usually not found outside the posterior pole, rarely are larger than the optic disc, disappear spontaneously within two months, and are asymptomatic. Some of these distinguishing features can be readily appreciated in the patient shown in Figure 7, who manifests both HIV retinopathy and CMV retinitis. In cases where the two lesions are not so easily distinguished, the lesion(s) should be observed for progression over the course of several weeks. If it abuts the fovea or optic disc, such delay is inadvisable, and fluorescein angiography can be used to differentiate an active CMV lesion (leaks fluorescein) from a cotton-wool spot (no leakage). The patient shown in Figure 8 displays a lesion near the fovea that could be an early focus of retinitis. Because the lesion is in close proximity to the fovea and might threaten central visual acuity if it were infectious, a fluorescein angiogram was obtained. In this case, the angiogram showed no leakage of dye, indicating that this is probably not an infectious or inflammatory focus but probably a cotton-wool spot due to benign microangiopathy.

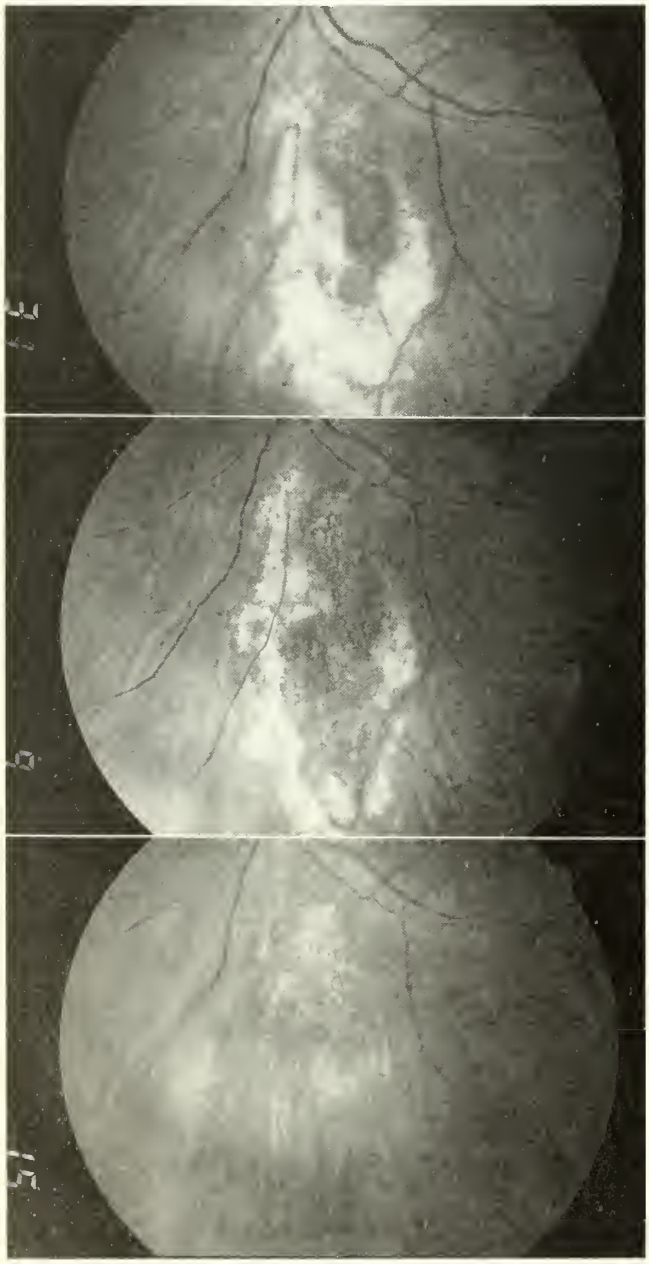

Figure 9.—A positive response of a cytomegaloviral retinal lesion to treatment with intravenous ganciclovir is demonstrated by serial fundal photography. **Top,** The pretreatment appearance of the lesion is shown. **Middle,** Two weeks after treatment was instituted, the lesion borders are less edematous and hemorrhagic and have not advanced. **Bottom,** After 6 weeks, the lesion is essentially healed; the previously involved retina is atrophic and nonfunctional.

Ganciclovir is active against all herpesviruses and is an approved agent for the treatment of CMV retinitis. The drug is taken up by host cells and phosphorylated by host-cell kinases. The phosphorylated compound then competitively inhibits only viral DNA polymerase, so that DNA synthesis in noninfected cells is spared. Ganciclovir halts progression or induces remission in 80% to 100% of patients, although recurrence and progression after several months are common, and reinduction or dose adjustments based on renal function may be required.[1,2,25]

The current use of ganciclovir usually includes a loading dose of 5 mg per kg given intravenously every 12 hours for 14 to 21 days (induction phase), followed by indefinite maintenance therapy at 5 mg per kg given once a day every day.[25-27] At many institutions, patients are instructed to administer the infusion at home through a permanent intravenous catheter typically placed at the beginning of treatment.

A clinical response is evidenced by a decreased whitening of the active lesion, usually within two to three weeks, and by failure of the border to advance. Areas of retina that have already been destroyed, and the associated vision loss, do not return with treatment. A series of photographs (Figure 9) taken over the first six weeks of ganciclovir administration shows a typical treatment response, with failure of the active border of the lesion to advance, followed by decreasing edema and hemorrhage.

The side effects of ganciclovir therapy include granulocytopenia, neurologic dysfunction, abnormal liver function test values, and, rarely, thrombocytopenia. The most serious toxic effect is neutropenia, which may occur in as many as a third of patients when defined as less than 500 neutrophils $\times 10^6$ per liter (<500 per μl).[28] Granulocytopenia is generally reversible and may dictate dose reductions or discontinuation. It is exacerbated by the concurrent use of zidovudine, which has additive bone marrow-suppressive effects.[29] The concurrent administration of granulocyte-macrophage colony-stimulating factor or granulocyte colony-stimulating factor may protect against myelosuppression, and they are currently being evaluated in clinical trials.[30] Unfortunately, CMV retinitis is almost always reactivated within several weeks if ganciclovir therapy is discontinued; ongoing communication between the ophthalmologist and internist regarding therapeutic and unwanted effects of therapy is therefore critical.

In patients successfully treated with ganciclovir, one or more holes or tears can develop in areas of healed atrophic retina. These predispose to rhegmatogenous retinal detachments and further loss of vision. (Rhegmatogenous retinal detachments occur when fluid in the vitreous cavity enters the subretinal space through a retinal hole or tear, thereby lifting the retina from the underlying pigment epithelium.) We and others have reported incidences of retinal detachment of 15% to 30% in association with ganciclovir treatment of CMV retinitis[31,32]; detachment in CMV retinitis not treated with ganciclovir appears to be extremely rare.[33]

The repair of the detachment requires surgical therapy

(pars plana vitrectomy) with endolaser to reattach the retina, close all retinal breaks, and remove inflammatory membranes and scar tissue that place traction on the retina and the administration of a silicone oil to internally tamponade the detached retina against the eye wall.[31,32,34,35] Simpler detachment procedures, such as scleral buckling and pneumatic retinopexy, are associated with a high incidence of recurrence. Although anatomic reattachment of the retina is achieved in most instances and useful vision is often restored, postoperative visual acuity often deteriorates from progressive retinitis and recurrent or new detachments.

Foscarnet is an agent recently released for the treatment of CMV retinitis that inhibits DNA and RNA polymerases and reverse transcriptase; it thus possesses both anti-CMV and anti-HIV activity. Most patients with CMV infections will respond clinically to this drug as well.[36,37] Foscarnet also is given intravenously and, like ganciclovir, requires indefinite administration because the retinitis recurs if the drug is withdrawn. Side effects include nephrotoxicity, anemia, electrolyte disturbances, and neurotoxicity, including seizures.[36,37] Zidovudine can usually be given concurrently with foscarnet.

A recent multicenter clinical study compared ganciclovir with foscarnet in the treatment of CMV retinitis in patients with AIDS.[37] There was no difference between the treatment groups in the rate of progression of retinitis; however, the median survival was longer in the foscarnet group than in the ganciclovir group—12.6 versus 8.5 months—possibly because of foscarnet's antiretroviral activity.[38] Foscarnet is therefore gaining wider acceptance as first-line therapy for CMV retinitis in patients with normal renal function.

When discussing treatment options for CMV retinitis, the patient should be informed of the natural history of progression of the disease if left untreated, the irreversibility of vision loss from retinal necrosis, and the relatively high initial success rate of medical therapy. These factors must be weighed against the necessity for lifelong intravenous administration of medications, the placement of indwelling venous catheters, the possible incompatibility of treatment with the concurrent use of zidovudine, the risk for retinal detachment, and the myelosuppressive and other side effects that may limit therapy. Some of these concerns might be obviated by the use of intravitreal administration of ganciclovir. Multiple intraocular injections of ganciclovir have been successful in controlling CMV retinitis, but repeated injections given over several weeks are impracticable, potentially hazardous, and may cause retinal toxic effects.[25,39] Slow-release preparations for local ganciclovir delivery to the eye are under investigation, including a liposome-encapsulated drug and a surgically implanted intraocular delivery system.[40,41] Oral ganciclovir is currently being evaluated in clinical trials and may be a promising approach to the treatment of CMV infections.

Figure 10.—Herpes zoster ophthalmicus is shown in an immunocompromised patient. Involvement of intraocular structures by the virus is especially likely when there are vesicles in the distribution of the nasociliary nerve along the anterior lateral aspect of the nose (Hutchinson's sign), as shown.

Herpes Zoster Ophthalmicus

Herpes zoster ophthalmicus is ordinarily a disease of older or debilitated patients but is seen also in younger patients with immunodeficiency. We routinely inquire regarding risk factors for HIV infection in all young patients with herpes zoster ophthalmicus and recommend HIV-antibody testing in high-risk persons.[42,43] The external disease is diagnosed, as elsewhere on the body, by an erythematous, often vesicular, eruption within a dermatomal distribution. Frequently intense pain will precede the skin changes. If the ophthalmic branch of the trigeminal nerve is affected, the patient should be referred to an ophthalmologist to rule out ocular involvement. The risk of ocular disease is especially

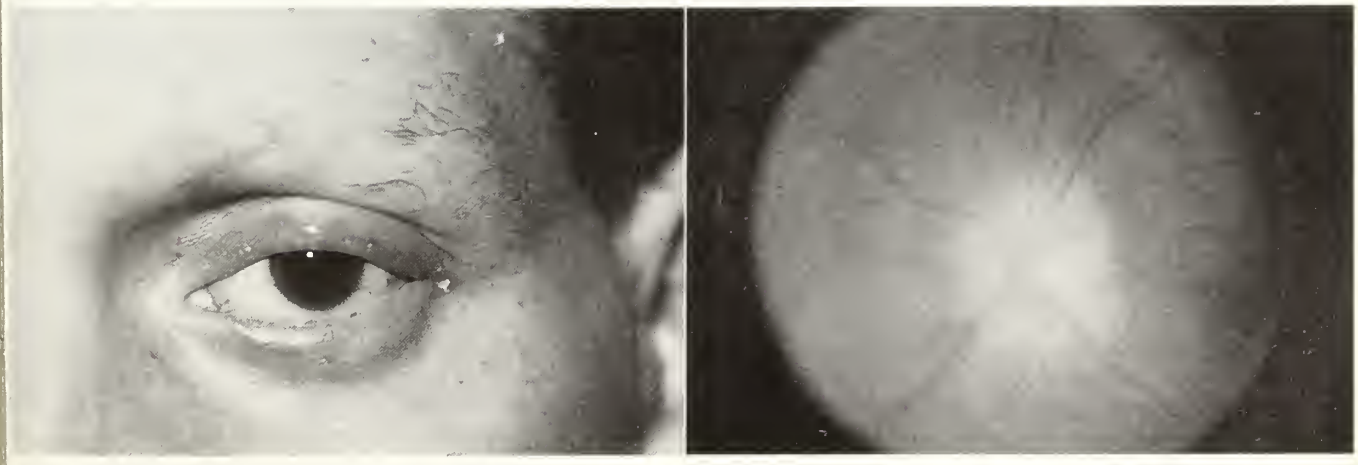

Figure 11.—Left, This 30-year-old man presented with lid erythema, loss of lashes, conjunctivitis, and a facial and palmar rash. On slit-lamp examination he had inflammatory precipitates on the posterior corneal surface and fibrinous pigmented connections between the iris and lens at the pupillary border. **Right,** Ophthalmoscopy showed vitritis, retinitis, and optic neuritis. Blood and cerebrospinal fluid specimens were positive for VDRL antigen. The patient was subsequently tested and found to be positive for the human immunodeficiency virus.

high if the nasociliary nerve is affected, indicated by lesions on the anterior lateral aspect of the nose (Figure 10). Herpes zoster ophthalmicus can affect all levels of the visual system, giving rise to dermatitis, conjunctivitis, keratitis, iritis or uveitis, vitritis, retinitis, optic neuritis, and encephalitis. Evidence of ocular zoster requires high-dose treatment with acyclovir, 10 mg per kg given intravenously three times a day for at least ten days. This disease may pursue a relatively more severe course in persons infected with HIV, and admission to hospital with intravenous therapy is recommended.[44]

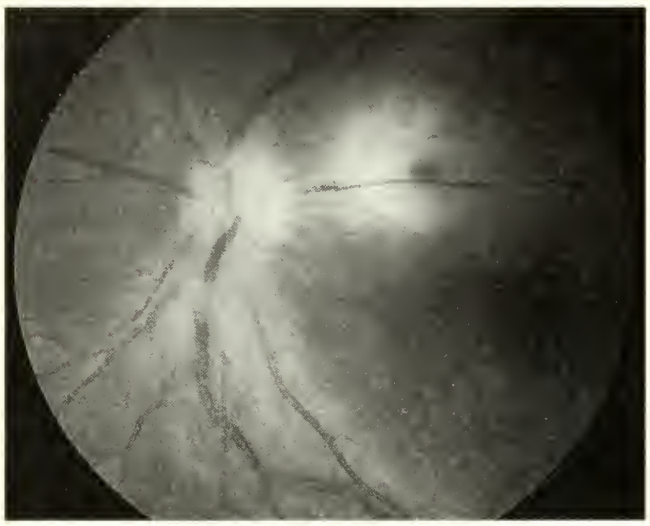

Figure 12.—A toxoplasmal retinitis lesion is shown along the superotemporal vascular arcade. The small grey choroidal scar just above the fovea suggests that the current episode involves reactivation of latent disease. There is serous retinal detachment present from extensive underlying vascular leakage. The view is hazy because of mild vitreous inflammation; severe vitritis obscures retinal detail, and the lesion appears as a "headlight in the fog." In patients with the acquired immunodeficiency syndrome, there may not be evidence of previous infection, and more extensive involvement may occur.

Syphilis

Often in the medical history of patients with AIDS, syphilis exhibits particularly severe reactivations of latent infection in immunocompromised patients.[45,46] Of note, because of the underlying disorder, serologic tests are occasionally falsely negative in these patients; biologic false-positive reactions for syphilis have rarely been reported in HIV-infected persons.[47] In the eye, syphilis may cause conjunctivitis, iritis, vitritis, retinitis, papillitis, and optic neuritis—in short, at any or all levels of the visual axis.[48,49] In some cases, the appearance of luetic retinitis as a focal expanding white lesion may simulate CMV retinitis, toxoplasmosis, or acute retinal necrosis.

In nonimmunocompromised hosts, ocular disease is usually associated with secondary syphilis, whereas in patients with AIDS, most patients with ocular symptoms harbor neurosyphilis as well[50]; thus, the presence of ocular manifestations demands a neurologic workup including lumbar puncture and therapy for neurosyphilis. The patient shown in Figure 11 had been treated by several physicians for persistent conjunctivitis; they failed to appreciate the loss of lashes typical of ocular syphilis and the palmar rash that suggests secondary syphilis. The slit-lamp examination reveals anterior chamber inflammation, and ophthalmoscopy shows an edematous retina and an inflamed optic nerve head; note also the haziness in the vitreous cavity, indicating considerable inflammation. This patient had syphilitic meningitis and was found during the hospital course to be HIV-positive.

Bacterial Infections

Bacterial conjunctivitis, keratitis, and retinitis have all been reported in patients with AIDS. Although the incidence of these infections may not be increased by concurrent infection with HIV—such infections have been generally described in case reports only—they may require more aggressive treatment. In HIV-infected patients who are also injectable drug users, severe bacterial and fungal intraocular infections may be metastatic, and systemic sources must be sought with appropriate cultures. Uncommon corneal pathogens, such as *Capnocytophaga* and *Microsporum* species have been reported to produce keratoconjunctivitis in immunocompromised patients.[51-53]

Cryptococcal Meningitis

Cryptococcal meningitis is the most common nonviral neurologic infection in patients with AIDS.[2] The visual system is commonly involved (in about 40% of patients with meningitis) by intracranial disease of the optic nerves or tracts, the third, fifth, sixth, or seventh cranial nerves, by extension of the disease process along the arachnoid sheath of the optic nerve and into the orbit,[1,2,54] and by metastatic involvement of the choroid.[10] The diagnosis of cryptococcal meningitis is suggested by the findings of visual field loss, cranial nerve palsies, or optic nerve swelling.

Toxoplasmosis

Toxoplasmosis in the eye usually occurs owing to reactivation of a latent congenital infection; in AIDS patients, however, it is generally newly acquired or newly disseminated from nonocular sites of disease.[20] It can occur alone or,

Figure 13.—Kaposi's sarcoma is a highly vascular tumor that has a predilection for the conjunctivae. The tumor typically presents as a nonclearing subconjunctival hemorrhage or as a fleshy red mass in the conjunctival fornix, as shown.

much less frequently, in association with the much more common central nervous system toxoplasmal lesions. The ocular picture, which consists of a dense vitritis and multifocal lesions of focal retinitis, has been described as a "headlight in the fog" appearance (Figure 12). The ocular disease typically resolves with the standard treatment of pyrimethamine and sulfadiazine or clindamycin.[55] Maintenance therapy is generally given because ocular toxoplasmosis in patients with AIDS frequently recurs when medical therapy is terminated.[20,55] Parenteral and topical steroids are some-

times added to reduce ocular inflammation after antibiotic administration is begun, although this should be done with caution in HIV-infected persons.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy is a diffuse papovaviral leukoencephalitis that may occur in patients with AIDS. Several visual deficits have been associated with this disorder, including diffuse vision loss, homonymous hemianopia, nystagmus, ocular motility defects, and optic neuropathies.[56,57] Thus, although progressive multifocal leukoencephalopathy lacks pathognomonic ocular features, it must be considered a possible cause of vision changes in any patient with dementia and corticospinal signs.

Kaposi's Sarcoma

Kaposi's sarcoma may involve the eye in about 20% of patients who manifest this highly vascular tumor.[2,58,59] It may be found along the lids or the conjunctivae and is especially common in the fornices and the palpebral conjunctiva (Figure 13). The initial symptoms may relate to the appearance of a subconjunctival hemorrhage, diplopia, blurring due to induced astigmatism, and, rarely, pain. The lesion need not be treated unless there are substantial symptoms or cosmetic concerns, in which case excision or radiation therapy with or without chemotherapy is often palliative.

Lymphoma

Lymphoma may rarely occur in the orbit of patients with AIDS and is suggested by proptosis, diplopia, pain, or periorbital swelling.[2,58-60] Intraocular lymphoma is occasionally associated with central nervous system lymphoma and may antedate or follow the brain lesion by several months.[61] Either diagnosis must be considered in patients presenting with neuro-ophthalmic signs with or without focal neurologic deficits.[61,62] Retinal and choroidal infiltrates and vitreous seeding in intraocular lymphoma may masquerade as an inflammatory condition or an infection such as syphilitic or candidal retinochoroiditis.[62] Primary intraocular lymphoma is rarely associated with AIDS.[60]

Ophthalmologic Referral

Indications for ophthalmologic referral depend in part on the experience of the primary care physician. In general, any loss of vision demands examination by an ophthalmologist whether or not the primary physician discovers objective findings; if vision loss is acute, severe, or progressive, consultation should be on an urgent basis. Ocular examination may establish diagnoses in patients with systemic disease of an unclear origin—for example, with tuberculous uveitis or disseminated *P carinii*. Patients with visual symptoms or pupillary changes and a central nervous system infection, such as toxoplasmosis or neurosyphilis, should be referred for fundus examination. Finally, any suspicious lesions noted with a hand-held ophthalmoscope, if not readily identified, should be discussed with an ophthalmologist. Infection with HIV per se is not an indication for referral, and a patient infected with HIV without ocular complaints does not require baseline or periodic ophthalmologic examinations. Children infected with HIV are susceptible to the same ocular diseases as adults, and the considerations outlined in this article apply also to them.

Patients with known CMV disease (colitis or pneumonitis) are at increased risk for CMV retinitis,[11,63] as are patients with $CD4^+$ counts below 50×10^6 per liter (50 cells per μl).[64] Increased vigilance on the part of primary care physicians for visual signs and symptoms is thus critical in these patients; however, periodic dilated eye examinations beyond an initial screening ophthalmologic visit are probably not warranted in asymptomatic persons.

Conclusion

The acquired immunodeficiency syndrome can manifest, and on occasion present, with a wide variety of ocular diseases. The primary caretaker of patients infected with HIV, by employing basic skills in ophthalmologic examination and an increasing knowledge of ocular signs, symptoms, and disorders, can better evaluate and counsel these patients when they have visual complaints.

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Articles

Suggested Guidelines for Rating Cardiac Disability in Workers' Compensation

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Cardiac disability ratings in workers' compensation cases currently lack any consistent scientific basis, with varying medical evidence used by different examiners in the same case. Opinions about the extent of disability may differ with the same patient, delaying resolution and the delivery of benefits. We describe guidelines for determining cardiac impairment and suggest a schedule for rating disability based on evidence. Our experience is in California, but arriving at equitable ratings for disability purposes is a nationwide challenge.

Exercise stress testing provides the best reproducible data to test the heart's ability to do work. When exercise stress testing is not possible or adequate, alternative or supplemental testing is necessary. Certain conditions, such as hypertension, arrhythmias, coronary artery spasm, and a history of coronary artery operations or myocardial infarction, may affect "cardiac disability" but may not necessarily be reflected in exercise testing.

(Clark WL, Alpern HL, Breall WS, et al: Suggested guidelines for rating cardiac disability in workers' compensation. West J Med 1993 Mar; 158:263-267)

Workers' compensation laws provide benefits for permanent disability if a person is restricted or excluded from the job market because of limited function. Objective and subjective factors, prophylactic work limitations, or an inability to compete in the open labor market may lead to work restrictions and disability payments. Physicians do not have the last word.

Industrial accident commissions have disability rating specialists to interpret the disability schedule and to make recommendations about the extent of disability after decisions by administrative judges. Disability evaluation specialists are guided by legal definitions of subjective symptoms, which state that "minimal or mild" subjective symptoms constitute an annoyance only, "slight" symptoms mean there is some interference with the activity that produces symptoms, "moderate" symptoms markedly interfere with the activity, and "severe" symptoms mean the activity is precluded.

Eight guideline paragraphs have been adopted for evaluating disability of the lungs, heart, abdominal wall, and spine (Table 1).[1]

Cardiac disability ratings can be based on subjective reports of symptoms or estimates of limitations made by a patient, a physician, or both. These may vary considerably in the same case. With differing expert medical opinions, the question of the extent of disability frequently must be resolved through the full workers' compensation litigation procedure involving appeals to the Workers' Compensation Appeals Board, the District Court of Appeal, and occasionally the State Supreme Court.

In 1988 the Medical and Chiropractic Advisory Committee to the Administrative Director of the California Division of Industrial Accidents tried to develop guidelines allowing cardiac disability to be rated more objectively and consistently, with appropriate scientific medical criteria. Representatives of groups who participate in the functioning of the workers' compensation system were consulted as to nonmedical matters pertinent to workers' compensation rating systems for cardiac disability.

Guidelines for Evaluating Cardiac Impairment

Exercise Stress Testing

The advisory group decided that measuring the acceptable exertional level of sustained work—eight hours per day—relative to the maximum oxygen consumption (in liters per minute) was essential. The results of a literature search are shown in Table 2.[2-13] The subcommittee decided on 45% of maximum oxygen consumption as the upper limit for sustaining heavy work.

Exercise stress testing is currently the single most productive means of quantitating a worker's impairment. Protocols and guidelines for exercise testing on the treadmill using the Bruce protocol and bicycle ergometer have been documented by the American Heart Association,[14] Bruce,[15] Pollock,[16] and others. Results should be given in mets (metabolic equivalent system). Reports should also include any clinical signs or symptoms reported or observed, reports of ectopic ventricular or supraventricular activity, specific electrocardiographic (ECG) changes noted, and descriptions of and timing of development of symptoms such as dyspnea, angina, ischemic ECG changes, or arrhythmia. Blood pressure response to testing is also recorded.

The end point of exercise testing is vital in determining the safe level at which a person can work. It should determine either maximum capability or the point at which any of the symptoms and signs listed are developed. If the examiner

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does submaximal testing, for example, stopping at "90% of expected," 10% should be added to the mets level calculated from Bruce or other testing protocol tables. The examiner should specify which symptom(s) or sign(s) caused the testing to be stopped and fully explain why cardiac impairment, rather than some other condition, caused testing to be stopped. There is always the possibility that the person tested may not give full effort. If a person stops voluntarily before reaching what is considered maximum capability, the examiner should estimate what the actual testing end point should be, giving reasons. Important sections of the tracings must be enclosed with the report.

TABLE 1.—*The 'Guideline Paragraphs' Used for Evaluating Disability of the Heart in the California Schedule**

Paragraph	Standard Disability Rating, %†	Description
a	10	*Disability precluding very heavy lifting* contemplates that an employee has lost about a fourth of preinjury lifting capacity; a statement such as "unable to lift 50 lbs" is not meaningful; the total lifting effort, including weight, distance, endurance, frequency, body position, and similar factors, should be considered
b	15	*Disability precluding very heavy work* contemplates that an employee has lost about a fourth of preinjury capacity for performing activities such as bending, stooping, lifting, pulling, and climbing or other activities involving comparable physical effort
c	20	*Disability precluding heavy lifting* contemplates that an employee has lost about half of preinjury lifting capacity
d	25	*Disability precluding heavy lifting, repeated bending, and stooping* contemplates that an employee has lost about half of preinjury capacity for lifting, bending, and stooping
e	30	*Disability precluding heavy work* contemplates that an employee has lost about half of preinjury capacity for performing activities such as bending, stooping, lifting, pushing, pulling, and climbing or other activities involving comparable physical effort
f	50	*Disability resulting in limitation to light work* contemplates that an employee can do work in a standing or walking position, with a minimum of demands for physical effort
g	60	*Disability resulting in limitation to semisedentary work* contemplates that an employee can do work about half the time in a sitting position and about half the time in a standing or walking position with a minimum of physical effort, whether standing, walking, or sitting
h	70	*Disability resulting in limitation to sedentary work* contemplates that an employee can do work predominantly in a sitting position at a bench, desk, or table with a minimum of physical effort and with some degree of walking and standing permitted

*From State of California Department of Industrial Relations.[1]
†Ratings are modified administratively to take into account age and occupation.

Symptoms and signs indicating the testing end point are as follows:

- Onset of atrial fibrillation;
- Onset of ectopic atrial tachycardia;
- Progressive drop in the heart rate as exercise continues or if the systolic blood pressure falls 10 mm below a previously measured level as exercise continues;
- Progressive ST segment elevation or depression;
- Progressive widening of the QRS complex;
- Premature ventricular contractions with progressive increasing frequency as the exercise progresses;
- Ventricular tachycardia (three or more consecutive beats);
- Excessive blood pressure rise (230 to 250 mm systolic);
- Subjective symptoms of dyspnea, undue fatigue, or dizziness;
- Progressive anginalike pain that in the examiner's opinion is cardiac-related. The examiner must fully explain if chest pain alone is a criterion for stopping.

Musculoskeletal pain or discomfort may limit the continuance of test; the end point in this event is not valid for an evaluation of cardiac impairment.

Pulmonary function testing may be needed to rule out pulmonary factors contributing to decreased exercise tolerance.

When testing has been completed and the end point in mets has been determined, a "safe" effort can be predicted. After reviewing the pertinent literature (see Table 2), we decided that if the testing end point is related to a poor state of physical fitness, the maximum short-term (less than 15 minutes once a day) work exertion allowed may be 80% of the end-point level. If a person is tested after medical intervention for cardiac ischemia and is asymptomatic off the treadmill, the maximum short-term work exertion allowed may be 80% of the testing end point in mets. If the testing end point is related to signs or symptoms of cardiac distress, the maximum short-term work exertion allowed should be 70% of the end-point level. The sustained level of work exertion for activities through most of the workday should be set at 45% of the testing end point in mets.

Alternative or Supplemental Testing

Other testing may be used if there are medical circumstances in which exercise testing is not possible or if the

TABLE 2.—*Options on the Acceptable Exertional Level for Sustained (8 hours per day) Work, Relative to the Maximum Oxygen Consumption ($\dot{V}O_2max$) Determined by Testing*

Source, yr	Opinion of Acceptable Exertional Level
Astrand, 1960[2]	50% of $\dot{V}O_2max$ is upper limit for sustained heavy work
Muller, 1962[3]	20%
Bink, 1962[4]	33%
Ekblom et al, 1968[5]	33% to higher rates increase level of blood lactate
Astrand and Rodahl, 1977[6]	30% to 40% suggested
Lind and Petrofsky, 1978[7]	45% to 55% for work involving lifting
NIOSH, 1981[8]	33%
Nelms, 1982[9]	50% should be attempted only by highly trained workers, such as lumberjacks
Ilmarinen, 1984[10]	30% without breaks, 50% with breaks
Astrand, 1988[11]	40% to 45% by choice—more than 50% leads to body temperature rise above 38°C; at 40%, heart rate is 125/min for 20- to 29-year age group
Haskell et al, 1989[12]	No more than 50%
Kilbom, 1980[13]	Work at 60% to 80% not recommended for more than 20 to 25 minutes (for short-term exertion)
Haskell et al, 1989[12]	No more than 80% for short-term exertion

NIOSH = National Institute of Occupational Safety and Health

examining physician thinks the performance of exercise testing by the applicant was spurious. Alternatives may be used, for example, when there are musculoskeletal handicaps that prevent exercise testing or when pre-exercise ECG changes such as left bundle branch block or myocardial infarction may make interpretation of ECG changes with exercise testing difficult. Exercise testing might be contraindicated in the presence of an ejection fraction of less than 20% or when there are recurrent complex cardiac arrhythmias, unstable angina, uncompensated heart failure, or Holter monitor or ECG demonstration of silent ischemia.

When alternative or supplemental testing is being used, the physician should consider whatever data are available from tests previously done, with the physician's opinion as to the validity of these data included in the report. Additional testing may be needed but must be verified by the physician. Even when exercise testing has been done satisfactorily and the allowable mets level for work determined, the data from tests previously done or from the additional testing or the existence of other ratable factors may suggest that modification of the allowable mets level is appropriate. All testing, exercise, or alternatives should be done after treatment and with the examinee under continuing treatment. To control costs, alternative testing to exercise testing must be justified and not repeated if appropriate testing results are available in a patient's record.

The ejection fraction may be used to estimate cardiac impairment in the absence of exercise testing or to modify or validate medical opinion based on exercise testing. An impairment may be present even when the ejection fraction is normal, such as with coronary occlusion. Therefore, ejection fraction measurement should supplement rather than replace exercise testing.

Cardiac catheterization with the direct measurement of cardiac output and cardiac index is the most accurate method of determining the ejection fraction. This would not be done routinely for workers' compensation disability evaluation. If it has been done recently, the information provided would be valuable. The physician should explain why the data are, or are not, considered relevant.

Alternatively, ejection fraction may be calculated from the results of an echocardiogram or a multigated angiogram (first-pass determination). Normal results should be stated. An ejection fraction of more than 55% is considered to be in the normal range, equivalent to cardiac performance to normal levels for age and sex. An ejection fraction of 45% to 55% represents slight impairment, 30% to 45% is moderate impairment, less than 30% is less than severe impairment, and less than 20% is severe impairment or total disability.

Information from the history may supplement exercise testing: activity levels reported can be translated into mets, previous exercise testing, or documented levels of exercise testing after injury, or documented levels of exercise programs in mets.

To determine if a person's injury is permanent and stationary, the current mets level must be compared with one taken earlier. One of these values should be used in this order:

1. Previous measurements by exercise testing;
2. If (1) is not available, translate activity within the past 5 years into mets;
3. If (1) and (2) are not available, translate nonwork activity into mets;

TABLE 3.—*Maximum Oxygen Uptake ($\dot{V}O_2max$) in Healthy 'Normal' Volunteers*†*

Age, yr	*Meon $\dot{V}O_2max$, ml/kg/min*	*10th Percentile*	*Mean*	*90th Percentile*
Men, mets				
20-29	39	9.0	11.0	13.5
30-39	37	8.6	10.5	13.2
40-49	35.7	7.8	10.0	12.8
50-59	33	7.0	9.4	12.4
60+	29	5.7	8.2	11.7
Women, mets				
20-29	30.2	6.2	8.6	10.8
30-39	30.2	6.2	8.6	10.2
40-49	26.7	6.0	7.6	10.0
50-59	24.5	5.0	7.0	9.4
60+	21.8	4.5	6.2	8.6

*Data from the Cooper Clinic Coronary Risk Factor Profile Charts, based on standards established at the Institute for Aerobics Research, Dallas, Texas, 1978 (from Pollock et al16).
†Maximum oxygen uptake was estimated from treadmill time.

4. If (1), (2), and (3) are not available, use the mean standard mets for age and sex from Table 3.[16]

Other notable factors such as coronary artery spasm, arrhythmias, cardiomyopathies, and hypertension should be described if they are present.

Coronary artery spasm must be diagnosed by ECG or Holter monitoring with ST segment changes elevated or depressed more than 1 mm. The Holter monitor must be a high-fidelity type and not a standard or event monitor. Important sections of the tracings, including scale and a technical description of the equipment used, should be included with the report.

The described level of emotional or physical stress, or both, producing spasm and subjective evaluation determine the extent of impairment. Nearly daily episodes of coronary artery spasm not controlled with medication represent severe impairment, episodes every week or two despite medication represent moderate impairment, and occasional episodes despite medication represent slight impairment.

Another factor of impairment may be the continuing need for medication. The examiner should describe the medication and any possible side effects, give their cause, and tell what if any restrictions are appropriate because of the side effects. If there are no notable side effects from the medication, this should be mentioned.

Arrhythmias should be evaluated after appropriate treatment and documented by data from ECG or Holter monitoring.

- On the treadmill, arrhythmias serve as end-point indicators and establish the impairment level.
- Occasional unifocal premature ventricular contractions with otherwise normal heart sounds represent no impairment unless temporarily related to stress or if a patient is preoccupied with symptoms.
- Ventricular arrhythmias in the presence of ventricular dysfunction or abnormality are associated with an increased risk of sudden cardiac death.
- Supraventricular arrhythmias may result in impairment related to the extent of subjective symptoms.

Cardiomyopathies of any cause are evaluated by exercise testing or by alternative testing if this is not possible, to determine the activity level allowed.

Hypertension is defined as a resting blood pressure of 140/90 mm of mercury or higher.[17] Controlled hypertension means a blood pressure at or lower than 140/90 mm of mercury. Incompletely controlled hypertension means an intermittent elevation of blood pressure higher than 140/90 mm of mercury. Uncontrolled hypertension means a blood pressure always higher than 140/90 mm of mercury.

With uncontrolled hypertension, treatment is needed, and the examinee may or may not be considered temporarily partially or totally disabled, pending such treatment.

In most persons, hypertension can be controlled with effective treatment. The medications and dosage as well as increases needed should be noted. Side effects may warrant an impairment rating and should be described and quantified, with their relationship to the medication explained.

During the testing of a person with controlled hypertension by ambulatory blood pressure monitor or treadmill, intermittent loss of control may be demonstrated. The level of physical or emotional stress producing loss of control may be a basis for an impairment rating. If there is end-organ damage with controlled hypertension, the examiner should describe and give the significance of it.

TABLE 4.—*Method of Calculating Disability Rating*

Step 1 Find the share of job market loss; this is the uncorrected disability rating

Column 1 If mets Capacity for Sustained Work (45% of test end) Is	Column 2 % Share of Job Market Loss Is*
5.0	10
4.3	20
3.8	30
3.4	40
3.0	50
2.6	60
2.2	70
1.9	80
1.5	90

Step 2 Find the share of job market loss related to age and sex; subtracting this figure from the uncorrected disability rating gives the corrected disability rating—the disability percentage not due to age and sex

Column 3 45% of Mean 'Normal' (for age and sex) $\dot{V}O_2$max† Is		Column 4 % Share of Job Market Loss Related to Age and Sex Is	
Age, yr	*Men, mets*	*Women, mets*	*Men, %*	*Women, %*
20-29	5.0	3.9	10	25
30-39	4.7	3.9	13	25
40-49	4.5	3.4	15	38
50-59	4.2	3.2	19	46
60+	3.7	2.8	32	53

Step 3 The corrected disability rating may be amended by considering the presence of coronary artery spasm, arrhythmias, hypertension, emotional stress, myocardial infarct, or cardiac surgery

Step 4 The corrected disability rating represents combined cardiac and pulmonary (if any) disability; apportionment may be appropriate after determining pulmonary disability by other means

Example: Supposing the mets capacity of a 35-year-old man for sustained work (column 1) is determined to be 3.4 mets. This excludes that person from 40% of the job market (column 2). 45% of the mean "normal" mets capacity for a 35-year-old man is 4.7 mets (column 3), which means that a "normal" 35-year-old man is on the average excluded from 13% of the job market (column 4). 40% minus 13% equals 27% loss of job market that is not due to age and sex, so 27% is the disability rating attributable to the heart impairment. This percentage may be modified as in steps 3 and 4.

*From the California State Employment Development Department,[18-22] and Passmore and Durnin.[23,24]

†Calculated from Table 3

Reaction to Emotional Stress

The relationship between emotional stress and heart disease is debated. Work restrictions to avoid emotional stress are regularly given and may constitute a disability. If the examiner thinks a preclusion from emotional stress is appropriate, the degree of the emotional stress to be precluded may vary, and thereby the degree of disability will vary. Physicians should specify examples of emotional stress to be avoided by the person examined, based on the person's experience.

Prophylactic restriction against all emotional stress might be given, for example, for recurrent complex cardiac arrhythmias persisting despite appropriate treatment; unstable angina or resting angina at a frequency of three or more times a week as documented by history; uncompensated heart failure; or ECG demonstration of silent ischemia persisting despite appropriate treatment documented by Holter monitoring and a diary.

Prophylactic restrictions against undue or more than ordinary emotional stress might be given for persons with occasional episodes of complex arrhythmias or arrhythmias associated with undue or more than ordinary emotional stress documented by Holter monitoring and a diary; angina with undue or more than ordinary stress; compensated heart failure; hypertension shown to become uncontrolled—with diastolic blood pressures above 100 mm of mercury more than half of the time—under undue or more than ordinary emotional stress; or ECG demonstrations of silent ischemia under undue or more than ordinary emotional stress documented by Holter monitoring and a diary.

Prophylactic restrictions against extreme emotional stress might be given for persons with arrhythmia precipitated by severe emotional stress documented by Holter monitoring and a diary; angina precipitated by severe emotional stress; worsening congestive heart failure precipitated by severe emotional stress; hypertension that becomes uncontrolled by severe emotional stress; or ECG demonstration of silent ischemia with severe emotional stress documented by Holter monitoring and a diary.

Disability Rating

Following the preceding Guidelines for Evaluating Cardiac Impairment, the physician examiner should summarize the evidence for the six possible factors of impairment (Table 4).[18-24]

The physician may interpolate between the levels in Table 4. Consideration should be given to the need for maximum short-term effort—less than 15 minutes once a day—in certain occupations. The 80% or 70% (see guidelines) level in mets of the person's testing end point should meet or exceed this maximum short-term mets requirement. Also, guidelines for evaluating cardiac impairment due to coronary artery spasm, arrhythmias, hypertension, emotional stress, and a documented history of myocardial infarction, coronary artery operation, or coronary angioplasty, as mentioned earlier, should be considered (see step 3, Table 4). All rat-

ings are "standard," subject to modification for age and occupation.

The summary of medical evidence prepared, as described here, will make it possible to rate a person's disability accurately. If there is disagreement between examiners about the evidence, the adjudicator can easily compare two or more summaries to determine which one has the more credible evidence or which points of disagreement should be explored further. Physicians experienced in workers' compensation, who may themselves wish to attempt disability ratings, will find the summary of evidence gives a logical, scientifically sound basis for such ratings.

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Articles

Listening and Talking to Patients
A Remedy for Malpractice Suits?

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This study evaluates the hypothesis that the way physicians communicate with patients and the degree patients perceive physician fault for bad medical outcomes are risk factors for the initiation of malpractice lawsuits. The study involved 160 adults who viewed a videotape of a physician treating a patient while using either positive or negative communication behaviors. Participants were told that the case had either a positive result, a bad result through no fault of the physician, a bad result for uncertain reasons, or a bad result that was the physician's fault. Participants then rated their litigious feelings.

Results showed that the use of negative communication behaviors by the physician increased litigious intentions. An increased perception of physician fault for the bad result also increased litigious intentions. Uncertainty as to the reason for the bad outcome, however, raised litigious feelings nearly as much as did perceived physician fault. The results of the study support the hypothesis that altering the way physicians communicate and improving patient education can affect the risk of malpractice lawsuits.

(Lester GW, Smith SG: Listening and talking to patients—A remedy for malpractice suits? West J Med 1993 Mar; 158:268-272)

How to prevent malpractice lawsuits continues to be an important concern for health care professionals. Although professional competence in medical practice is essential, studies have repeatedly shown that the quality of medical care is poorly correlated with the occurrence of malpractice lawsuits.[1-8] These data suggest that other factors are involved in triggering them. Many writers have speculated that two important risk factors for the initiation of malpractice lawsuits are the "quality of communication" between physicians and patients[1,2,5,9-11] and the perception that the physician is at fault for a bad result.[2,12,13] These factors may create a desire on the part of patients to strike back against their physicians, regardless of the practitioner's competence. The present study was designed to evaluate the validity of these speculations, which have not previously been tested experimentally.

Subjects and Methods

Participants in the study were 160 adults recruited from adult classes at two local community colleges and a local volunteer network. Participants were not required to have any particular level of experience with health care professionals and volunteered for the study in response to an invitation to participate in a research project that involved "viewing a videotape and completing a questionnaire." No other information about the topic of the study was provided until the beginning of each testing session, when participants were told that the study involved "physicians and medical treatment" and the presentation of a hypothetical medical case. Before participating, they were asked to complete an informed-consent form and were given permission to end their participation in the study at any time. Only one participant did not complete the testing sessions and was replaced with another.

We conducted the study in classrooms and meeting rooms with groups of participants. To minimize possible experimenter-bias effects in conducting the testing sessions, all instructions were provided in written form, and during the videotape viewing and questionnaire completion, the experimenter stood silently in the back of the room, out of sight of the participants. A video monitor used to show the videotapes was operated by remote control.

Participants were randomly assigned, by a coin toss, to one of two experimental groups, each of which viewed a different videotape of a hypothetical medical case in which a patient sees a physician for an office visit. One videotape showed the physician using "positive communication behaviors," including eye contact, a friendly tone of voice, presentation of information and requests for information, smiling, appropriate physical touch (shaking hands), self-disclosure, acknowledgment of verbalizations, reflections of affect, appropriate praise, and a relatively long period of contact (videotape length, 5 minutes 25 seconds). The second videotape showed the physician using "negative communication behaviors," including no eye contact, harsh and clipped tones of voice, criticism, a minimal presentation of information and minimal request for information, nonsmiling expressions, no friendly physical contact, no acknowledgment of verbalizations, no reflection of affect, no praise, and a relatively short period of contact (videotape length, 2 minutes 2 seconds).

In both videotapes, the patient described an identical complaint: "I have a mole on my neck that has started to itch and burn and has started to worry me," the physician made an identical diagnosis: "It's an angioma," and the physician performed an identical treatment: a subcutaneous injection and a prescription for antibiotics. The same medium-height,

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approximately 35-year-old white male actor portrayed the physician in both videotapes, and the same medium-height, approximately 35-year-old white female actor portrayed the patient in both videotapes. Both videotapes were filmed in the same dermatologist's examining room, from the same camera angle, with the physician dressed in the same clothes and white coat and the patient dressed in the same clothes.

After viewing the videotape, participants read one of four "Case Outcome Reports," distributed in a blind manner by the experimenter. The first report stated that the result had been good (detailed as the spot clearing up and healing normally, without subsequent ill effects). The second report

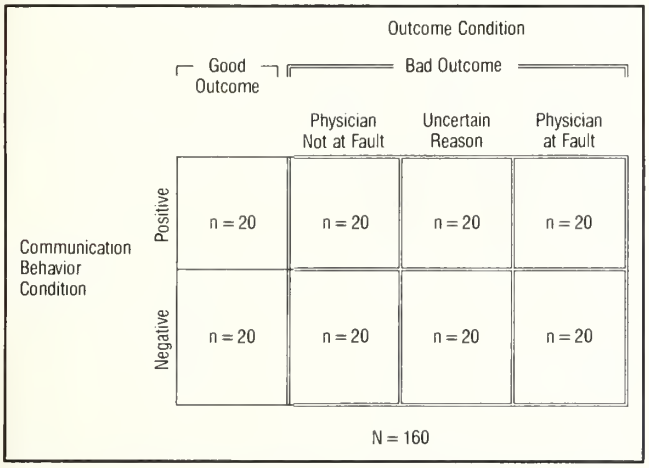

Figure 1.—The schema illustrates the overall experimental design: Communication behavior (positive or negative) is examined in relation to good and bad outcomes (no physician fault, uncertain, and fault).

stated that the physician was clearly not at fault, but there had been an unforeseeable and unpreventable bad result (detailed as worsening of the condition, substantial discomfort and pain, the necessity for further medical treatment, and substantial scarring and disfigurement). The third report stated that it was uncertain whether or not the physician was at fault but that there had been a bad result (detailed identically to that in the second report). The fourth report stated that the physician did not diagnose and treat correctly and was at fault for a bad outcome (also detailed identically to that in the second report).

After reading one of the four reports, all participants completed a four-page questionnaire specifically designed for this study to be as clear and simple as possible to minimize complexity and nuances and maximize potential reliability. The questionnaire required an average of about seven minutes to complete and consisted of ten questions. On a scale of 1 (least) to 10 (most), participants were asked to rate how professional, caring, friendly, trustworthy, and competent the physician was, how severe they found the outcome to be, how much they considered the physician to be negligent, liable, and to blame for the result, and how likely they would be to file a lawsuit against the physician. The questionnaire also solicited demographic data—age, sex, marital status, religious preference, ethnicity, and occupation. Participants were then debriefed, given the opportunity to ask questions, and excused.

Results

To minimize possible experimenter bias in data analysis, the experimenter not involved in conducting the testing sessions coded the data and the other experimenter entered the data into the computer and did the statistical analyses. A few participants skipped answering an occasional question on the questionnaire, so sample sizes vary slightly from analysis to analysis, and there is a slight variation in the degrees of freedom in different analyses.

Analysis of the demographic data showed that participants had an average age of 39, an average education of 14 years, and 82% were women. A univariate analysis of variance done on each demographic variable revealed two differences between experimental groups: more participants assigned to the negative communication behavior than the positive communication behavior condition were married ($F[1, 142] = 11.37$, $P \leq .001$), and their average age was younger—means of 36.7 years versus 41.7 years, respectively ($F[1, 142] = 6.83$, $P \leq .01$). No other differences were found.

The experimental design crossed two levels of communication behavior (positive, negative) with the good result and three levels of physician fault for bad result (no fault, uncertain, fault), resulting in a 2×4 factorial design (Figure 1). Because a bad medical outcome is presumed to be required to reliably create litigious feelings, the good result was included in the study to establish whether the three outcome reports detailing a bad medical result successfully induced a sense of a bad result for the participants. This question was examined by using a t test to compare participants' ratings of severity of outcome between the good outcome and the bad ones. The test, using a two-tailed probability and a separate variance estimate, was significant: $t(42.55) = 15.11$, $P \leq .001$. This indicated that the experiment succeeded in inducing a sense of a bad result for participants in the bad-outcome conditions.

We also presumed that a consistent sense of the severity of the bad result across all bad-outcome conditions was desirable because this would indicate that the independent variables of communication behavior and perceived physician fault were not contaminated by differences in perceptions of the severity of outcome. Using a 2×3 analysis of variance on ratings of severity of results for the six bad-outcome cells, we found neither significant main effects nor significant interaction effects (Table 1), indicating that the perception of the

TABLE 1.—*Analysis of Variance: Ratings of 'Severity of Outcome' in Bad-Outcome Condition: Communication Behavior (Positive, Negative) Versus Physician Fault (No Fault, Uncertainty, Physician Fault)*

Source	Analysis of Variance df	MS	F*
Communication behavior	1	.18	.19
Perceived physician fault	2	.56	.60
Interaction	2	1.54	1.64
Residual	112	.93	--

MS = mean square

*No significance found.

severity of outcome did not differ significantly between experimental groups. Because these analyses completed the intended use of the good result condition and the severity of outcome rating, we excluded both from subsequent hypothesis testing.

To test the hypothesis that the use of good communication

TABLE 2.—*Analysis of Variance: Ratings of How Professional, Caring, Friendly, Trustworthy, Competent, to Blame, Negligent, and Liable Physician Is and How Likely Participant Would Be to Sue in Bad-Outcome Condition: Communication Behavior (Positive, Negative) Versus Physician Fault (No Fault, Uncertainty, Physician Fault)*

		Professional		Caring		Friendly		Trustworthy		Competent	
Source	df	MS	F	MS	F	MS	F	MS	F	MS	F
Communication behavior	1	486.62	105.99*	1002.36	333.91*	1495.37	609.64*	465.08	137.87*	317.00	80.19*
Physician fault	2	13.30	2.89	8.44	2.81	1.14	.46	16.80	4.98	20.38	5.15
Interaction	2	10.28	2.41	9.35	3.11	1.50	.61	9.40	2.78	1.63	.41
Residual	113	4.59		3.02		2.45		3.37		3.95	

	To Blame		Negligent		Liable		Likelihood of Suing	
Source	MS	F	MS	F	MS	F	MS	F
Communication behavior	58.33	13.78*	134.10	29.24	76.39	13.10*	77.04	9.36†
Physician fault	64.56	15.25*	56.83	12.39	84.34	14.37*	44.04	5.35‡
Interaction	.97	.22	1.43	.31	7.97	1.35	15.45	1.87
Residual	4.23		4.58		5.87		8.22	

MS = mean square

*$P \leq .001$. †$P \leq .01$. ‡$P \leq .05$.

behaviors decreases the likelihood of a lawsuit and increases positive perceptions of a physician when a bad outcome occurs, we examined the communication behavior main effect of a 2×3 factorial multivariate analysis of variance (MANOVA) done on all bad-result conditions. The multivariate test, Wilks' lambda, was significant: $F(1, 113) = 72.74$, $P \leq .01$. A subsequent univariate analysis of variance, with the significance level partitioned across the nine analyses, was done on each dependent variable (Table 2). These tests show that participants were significantly more likely to sue physicians who used negative communication behaviors and also to rate them as less professional, caring, friendly, trustworthy, and competent and significantly more to blame, more negligent, and more liable.

Another hypothesis—that an increased perception of physician fault for a bad result increases litigious intentions and decreases positive perceptions of a physician—was tested by examining the perceived-physician-fault main effect in the 2×3 MANOVA used in evaluating the previous hypothesis. The result was significant: $F(2, 112) = 2.27$, $P \leq .01$. A subsequent univariate analysis of variance, with the significance level partitioned across the nine analyses, was done on each dependent variable (Table 2). These tests again confirmed our hypothesis.

Would increases in litigious feelings and a decrease in positive perceptions of a physician occur at each level of increase in probability of physician fault? This question was analyzed by using Hotelling's T^2 for two tests: comparing the no-physician-fault condition to the uncertain condition and comparing the uncertain condition to the physician-fault condition. The significance levels were partitioned across the two comparisons. The test for no fault versus uncertain was significant: $F(9, 67) = 2.44$, $P \leq .01$. Univariate t tests done on the dependent variables, using a two-tailed test and a significance level partitioned across the nine comparisons, showed that participants in the uncertain condition rated the physician as more to blame ($t[76] = 3.81$, $P \leq .001$), more negligent ($t[76] = 3.24$, $P \leq .002$), and more liable ($t[76] = 2.59$, $P \leq .01$). Ratings for how likely participants would be to sue the physician showed a trend ($t[76] = 2.59$, $P \leq .09$) but did not reach significance.

The multivariate Hotelling's T^2 test comparing the uncertain condition to the physician-fault condition was not significant: $F(9, 69) = .85$, $P \geq .05$.

Discussion

The results of this study support the hypothesis that the way physicians communicate is a risk factor for malpractice lawsuits. A physician relating to a patient in a "negative" manner triggered increased litigious feelings when there was a bad result, whereas a physician relating to a patient in a "positive" manner did not.

Other studies some 20 years ago similarly established that positive communication behaviors tend to strongly communicate caring and concern and to elicit positive and constructive responses.[14,15] Based on our study, the first to apply such methods specifically to physicians' behavior, it seems likely that positive communications would result in less litigiousness because the physician is viewed as having cared about the patient and thus having acted in good faith. In the world of relating, good faith counts for a lot: one's reading of good and bad faith tends to define who is a malicious villain and who is a fallible human being.

On the other hand, negative behaviors tend to communicate lack of concern and even antagonism and may be seen by patients as a violation of the unwritten but inherent "caring" nature of the physician-patient relationship. Long before there is any medical outcome to be concerned about, the patient may believe that the physician has already done something "wrong" simply by relating in what is perceived to be an uncaring manner. This may set the stage for later retaliation if something does go wrong.

We undertook a post hoc data analysis related to this interpretation. A univariate, two-tailed t test was used to compare the ratings of physician negligence between the conditions of positive and negative communication behaviors within the good-result condition. Because the good-result condition described a good medical outcome, differences in perception of the physician had nothing to do with any bad outcome; they were based entirely on communication behavior. The test was significant—$t(37) = 2.77$, $P \leq .01$—indicating that participants thought the physician using negative communication behaviors was more negligent than the physician using positive communication behaviors, even though there was no bad medical result. This is a post hoc data analysis, but it suggests that a subsequent bad medical outcome solidifies the perception of negligence and presents the opportunity and rationale for retaliation through a lawsuit.

How does communication behavior restrain litigious intentions? The data suggest that it may not simply be a function of inducing "nice" or "positive" feelings about the physician. First, litigious feelings are correlated with, but do not covary identically with, other perceptions of physicians (Table 3). Second, a review of cell means (Table 4) reveals that, whereas an interaction effect between communication behavior and perceived physician fault was not statistically significant in the overall MANOVA, the cell means for ratings of intentions to sue do not increase across the three fault conditions when positive communication behaviors were used, but the ratings of blame, negligence, and liability do. Although again this is a post hoc review of the data, it implies that positive communications restrain litigious feelings by a more complex process than presenting the physician in a "positive" manner. The physician was still seen as being more to blame, negligent, and liable for the bad result, even though there was no accompanying increase in the desire to retaliate.

It may seem self-evident that patients are less likely to sue a physician they perceive as caring, but, if so, it is difficult to explain why practitioners seem to perceive "bedside manner" as superfluous, bothersome, or simply irrelevant to the practice of competent and technologically sophisticated medicine. In fact, while conducting the current study, we were struck by consistent anecdotal data suggesting that even if practitioners do not feel that way, many people seem to think they do.

We were initially concerned that our portrayal of the negative communication behavior condition was excessive, given that the physician in the videotape showing negative communication behavior exhibits *all* negative communication behaviors and *no* positive communication behaviors. But during the study we heard dozens of off-hand comments about the videotaped scenes, none of which suggested that the negative communication behavior condition seemed unusual, harsh, or unrealistic. To the contrary, the reaction often seemed to be, "Well, that's just the way they are." Although this view may not be accurate or fair, it reflects a widely held opinion that physicians are uncaring and unkind.

The results of this study also support the hypothesis that perceived physician fault for bad outcomes raises litigation risk, although the increase occurred only when the fault was clear, not uncertain. This contrasts with the ratings for blame, negligence, and liability that increased between the no-fault and uncertain conditions, but not between the uncer-

TABLE 3.—*Correlation of Ratings of 'How Likely to Sue' With Other Perceptions of Physician*

Perception of Physician	How Likely to Sue Pearson r
How professional	−.32*
How caring	−.23†
How friendly	−.21†
How trustworthy	−.35*
How competent	−.52*
How much to blame	.73*
How negligent	.69*
How liable	.72*

*$P \leq .01$. †$P \leq .05$.

TABLE 4.—*Means for Cells in Bad-Outcome Condition: Communication Behavior (Positive, Negative) Versus Physician Fault (No Fault, Uncertain, Fault)*

Lawsuit Likely According to Perception of Behavior	Positive Communication Behavior			Negative Communication Behavior		
	No Fault	Uncertain	Fault	No Fault	Uncertain	Fault
Likely to sue						
Mean	5.16	5.90	5.90	5.21	7.90	8.50
SD	3.32	3.25	3.16	2.14	2.57	2.54
Professional						
Mean	7.25	5.35	5.50	2.10	2.20	1.65
SD	2.44	2.66	2.58	1.55	1.85	1.42
Caring						
Mean	7.78	5.90	7.05	1.05	1.10	1.15
SD	2.27	2.44	2.56	.22	.31	.49
Friendly						
Mean	8.63	7.95	8.45	1.15	1.25	1.35
SD	2.08	1.90	2.13	.36	.55	1.35
Trustworthy						
Mean	6.84	4.80	4.90	1.75	1.45	1.45
SD	2.31	2.40	2.71	.91	.69	.76
Competent						
Mean	6.10	4.85	4.30	2.40	1.65	1.40
SD	2.35	2.89	2.58	1.84	1.23	1.09
To blame						
Mean	5.00	6.74	7.10	6.05	8.25	8.75
SD	2.40	2.42	2.10	2.11	1.91	1.16
Negligent						
Mean	4.79	6.47	6.70	6.60	8.50	9.25
SD	2.59	2.50	2.36	2.11	1.85	1.12
Liable						
Mean	4.73	5.95	6.80	5.40	8.10	8.90
SD	2.72	2.89	2.65	2.89	1.83	1.45

tain and physician-fault conditions. Why negative perceptions but not litigiousness should increase with uncertainty as to fault is unclear. It may mean that inducing litigious feelings is simply more difficult than inducing negative perceptions and so may require a greater overall degree of difference in perceived physician fault. It may also be that because of the lack of resolution uncertainty creates, it is at least as upsetting for most people as knowing who is at fault. This kind of reaction can be seen in cases of "mysterious" misfortunes wherein people devote many years of their lives to trying to find out who or what is responsible for a particular tragedy or crime, even when nothing can be done about it.

Another possible interpretation of this finding is that people have unrealistic expectations concerning physicians and the state of medical science and are unwilling to believe that a bad result can occur without someone having done something wrong. Thus, they may blame someone even when there is really no one to blame. In either case, it seems to be another piece of bad news for physicians—that when there is uncertainty as to the reason for a bad outcome, they do not get the benefit of a doubt.

The results of our study support the idea that physicians may be able to affect their risk of lawsuits by changing the way they behave with patients. The use of good communication behaviors, for example, may not be technically more "competent" medicine, but it may prevent lawsuits, even when something has clearly gone wrong and even when it is clearly the physician's fault.

The study also suggests that patient education may reduce the frequency of litigation. When patients are informed enough to be certain that a bad result is not the physician's fault, negative perceptions and perhaps litigiousness remain low. At the same time, even though a well-informed patient may also be able to tell when the physician is at fault in a bad outcome, this knowledge seems to raise negative perceptions and possibly litigious feelings only a small amount beyond what occurs when the patient is uncertain about the reason for a bad outcome. As a result, there may be much to be gained and little to lose from having well-informed patients.

This study is relatively small and, as far as we know, the first to examine these variables in a controlled experimental setting. The whole issue is complex, difficult, and deserves much attention and research. The positive results of the present study suggest that attempts to lower litigation risk by using extra medical procedures and tests, consultation, and extensive documentation, often known as "defensive medicine," may miss the point. Although such efforts may be preventive in that their "double-checking" may help to avoid some bad medical results, they will not prevent them all. And when a bad result does occur, even lack of physician fault and the presence of extra procedures seem unlikely to diminish litigious feelings and the resulting chance of a lawsuit. Defensive medicine is not so much a tool to prevent lawsuits as it is to win them if they do occur. It can help provide the necessary courtoom evidence that a physician provided an appropriate standard of care. But if the intention is to prevent a lawsuit in the first place, forging a physician-patient bond that can effectively resist the pressures of our litigation-crazed and socially antagonistic society seems indispensable. An important way of accomplishing this may be through improving physician communication skills and patient education.

Perhaps Gregory best sums up our feelings when she says,

> An attitude of care and concern, a relationship that bespeaks thoughtful professionalism, and a humanistic approach many times solves more problems, melts more hostilities, and *eliminates more suits* than almost any other single recommendation [emphasis added].[5(p185)]

Acknowledgment

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Biomedical Science

Cancer Genes

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Cancer is a genetic disease; tumor cells differ from their normal progenitors by genetic alterations that affect growth-regulatory genes. There exist 2 classes of such cancer genes: the oncogenes, which function as positive growth regulators, and the tumor suppressor genes, which function as negative growth regulators. Oncogenes are widely conserved among diverse forms of life and are active in transmitting growth signals from the cell periphery to the cell nucleus. These signaling functions can be disturbed by many types of genetic change; the result of an altered growth signal is often cancer. Tumor suppressor genes have an attenuating effect on cell growth that is lost as a result of inactivating mutations or deletion of the gene; in DNA virus–transformed cells, it is abrogated by neutralization of the tumor suppressor protein through a viral gene product. Tumor suppressor genes were first recognized in inherited cancers; defects in a tumor suppressor transmitted through the germ line can lead to increased tumor incidence in the offspring. Tumor suppressors also play important roles in nonheritable cancer, however; many tumors in humans show defects in tumor suppressor genes.

Most cancers harbor multiple genetic changes in oncogenes as well as tumor suppressor genes. Oncogenes induce aberrant growth through a gain in function; tumor suppressor genes contribute to oncogenesis through a loss of function. Both types of mutation work together to produce cancer; the changes are not constant but increase in number as the tumor develops from benign to more and more malignant. Cancer results from the accumulation of genetic changes. Oncogenes and tumor suppressor genes provide important insights into the regulation of cell growth. This knowledge can now be used to develop gene-specific therapies for cancer.

(Vogt PK: Cancer genes. West J Med 1993 Mar; 158:273-278)

Research in the past 30 years has led to a convergence of ideas about cancer. By almost universal consensus, cancer is now viewed as resulting from changes in a few key regulatory genes. The disciplines of cancer research have also converged to focus on genes that regulate cell growth and differentiation. The major impulses for this remarkable development have come from virology. Viruses have been the tools of discovery for cancer genes, and virology has played a major role in transforming cancer research into a genetic science.

Two kinds of cellular genes are altered in cancer: positive growth regulators, called oncogenes, and negative regulators, referred to as tumor suppressor genes. The existence of cellular oncogenes was revealed through the study of retroviruses. Our understanding of tumor suppressor genes has been greatly advanced by their interactions with DNA tumor viruses. In this article I summarize the new molecular genetics of cancer and trace its origins back to the seminal work of two great pioneers, Peyton Rous and Theodor Boveri.

Retroviral Oncogenes

Retroviruses are RNA viruses that replicate by a unique mechanism: Their RNA genome is transcribed into DNA and inserted into the chromosomal DNA of the cell. The integrated provirus is then transcribed into viral messenger RNA and into progeny RNA genomes. Viral proteins made in the cytoplasm are assembled into viral particles that bud from the plasma membrane. As a rule, retroviruses do not kill the host cell but allow it to survive and may even transform it into a tumor cell.

The discovery of oncogenes was triggered by the simple observation that there are two kinds of retroviruses, those that transform cells in culture and induce tumors rapidly and those that do not transform cultured cells and are tumorigenic only after a long latent period. An exemplary pair of these two kinds of retroviruses is Rous sarcoma virus (RSV), which turns cultured chicken fibroblasts into tumor cells, and its close relative transformation-defective RSV (*td*RSV), which has lost this transforming potential for cells in culture. Both viruses are infectious and can multiply in chicken cells. The retrovirus RSV, however, contains an additional gene not needed for virus survival but required for tumorigenesis. This extra gene, the *src* oncogene, is absent from *td*RSV. Otherwise the genetic material of *td*RSV is identical to that of RSV and contains all information needed to direct the synthesis of retroviral progeny.

This simple difference between RSV and *td*RSV can be used to isolate DNA that is specific for the oncogene (Figure 1). In this isolation procedure, the RNA genome of RSV is transcribed enzymatically in the test tube into a single-stranded complementary DNA copy. The copied material is then allowed to bind to the RNA from *td*RSV. All complementary DNA will anneal to form a double-stranded DNA-RNA complex. The DNA of the *src* oncogene, however, has

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ABBREVIATIONS USED IN TEXT

Rb = retinoblastoma viral protein
RSV = Rous sarcoma virus
SV40 = simian virus 40
*td*RSV = transformation-defective RSV

no counterpart in the RNA of *td*RSV, and it remains single stranded in this reaction. The single-stranded nucleic acid can be separated from the double-stranded forms; the result is a DNA probe for the *src* oncogene. This complementary probe binds to nucleic acids having the same sequence information as *src* and, properly labeled, can therefore detect the *src* oncogene in any genetic material.

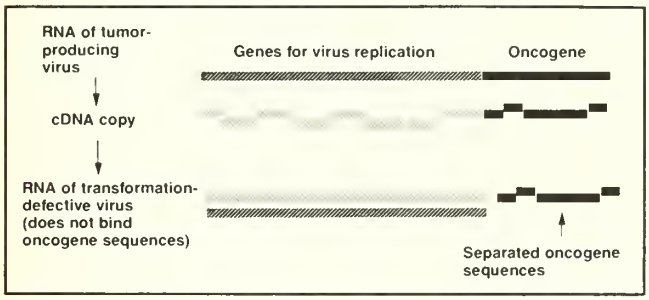

Figure 1.—The RNA genome of Rous sarcoma virus (RSV), a tumor-inducing retrovirus, is transcribed into complementary DNA representing the whole genome but consisting of numerous small pieces. The DNA is then allowed to anneal by base pairing to the RNA genome of *td*RSV, a nontransforming virus that lacks the *src* oncogene. All DNA will bind to RNA except those fragments containing *src* information. This single-stranded, complementary *src* DNA can be separated from the double-stranded RNA-DNA hybrid molecules.

A search with the *src* probe revealed the surprising fact that *src*, although carried by a virus, is originally a cellular gene. It is not only present in the cells of chickens, which are the natural hosts for RSV, but is conserved in the cells of all vertebrates. Similar probes have established a host origin for all other retroviral oncogenes. They are cellular, not viral, genes, accidentally incorporated into the viral genome and then transduced by the virus from cell to cell.

TABLE 1.—*Functional Classes of Retroviral Oncogenes*

Function	*Oncogene*
Growth factor	*sis*
Receptor tyrosine kinase	*erb* B
	fms
	ros
	sea
Signal protein	*ras*
Nonreceptor tyrosine kinase	*src*
	yes
	fps
	abl
Serine threonine kinase	*raf*
	mos
Cytoplasmic regulator	*crk*
Transcription factor	*jun*
	fos
	erb A
	rel
	ski
	myc
	myb

Oncogenes Function in Cellular Signal Transduction

The growth and division of cells is governed by external signals. These may be peptide growth factors or hormones that bind to and activate specific cellular receptors. Activated receptors then propagate the signal, either directly or through a series of sequential protein-protein interactions to the cell nucleus. In the nucleus, the signals are converted into programmed responses of the cell, consisting of specific patterns of gene expression. Most retroviral oncogenes code for protein components of the signal transduction chains that guide the signal from the cell periphery to its interaction with the cell genome (Table 1). Oncogenes code for growth factors, growth factor or hormone receptors, signal-transducing proteins, kinases that modulate the activity of key cellular enzymes, proteins that control kinases, and transcription factors that determine the levels of gene expression. These components of signal transduction are themselves subject to intricately balanced controls in the normal cell. A disturbance of these controls can have profound consequences for the growth properties of the cell and can lead to oncogenic transformation.

Various Kinds of Genetic Change Activate the Tumorigenicity of Oncogenes

As cellular genes, oncogenes can become deregulated by several kinds of genetic change (Figure 2). Transduction by a retrovirus places the expression of the oncogene under the control of viral promoter and enhancer sequences and introduces mutations in the oncogene that change the inherent activity of the gene product. Retroviruses can also activate the tumorigenic potential of an oncogene by inserting their dominant promoter and enhancer sequences near the cellular

Viral Oncogenes

- Retroviral transduction
- Promoter/enhancer insertion
- Transactivation

Nonviral Oncogenes

- Point mutation
- Amplification
- Chromosomal translocation

Figure 2.—The latent tumorigenicity of oncogenes can be activated by various kinds of genetic change. There are 3 retroviral mechanisms, of which transduction is the most efficient and promotor/enhancer insertion the most common. Transactivation may play an important part in the leukemia induced by the human T-cell leukemia virus, but final proof is still lacking. All 3 nonviral mechanisms have been found in human tumors.

oncogene and thereby increasing the expression of that gene. Some retroviruses, among them the human immunodeficiency virus and the human T-cell leukemia or lymphoma virus, may also increase the expression of cellular oncogenes by producing a transcription factor that alters gene expression when it interacts with specific gene regulatory sequences, including those of cellular oncogenes.

The latent oncogenicity of cellular oncogenes can also be activated by nonviral genetic changes. Mutations in the coding sequences of an oncogene can alter the response of the corresponding protein to regulatory molecules. Translocation of a cellular oncogene to another chromosome can bring the oncogene under the influence of strong cellular enhancer

regions that elevate its level of expression. Translocation can also activate the oncogenic potential of the oncogene by fusing it with another gene. Oncogenes can be amplified, and increased copy numbers of the gene per cell usually lead to increased amounts of the corresponding protein. All these mechanisms of deregulation have been found in tumors of animals and humans. The intervention of retroviruses is only one of several possible ways by which a cellular oncogene can become tumorigenic.

Human Tumors Harbor Activated Oncogenes

If DNA is extracted from human bladder carcinoma cells and introduced into normal mouse cells, the recipient cells undergo oncogenic transformation (Figure 3). The DNA responsible for this transformation has been identified as a mutated human version of the *ras* oncogene, a gene known from a tumor-producing murine retrovirus. The mutated human *ras* acts as a dominant transforming gene. Its product prevails over the regulated, cellular form of *ras*. Oncogenic mutations in *ras* are common in many human tumors, especially carcinomas of the colon, the urinary bladder, and lungs.

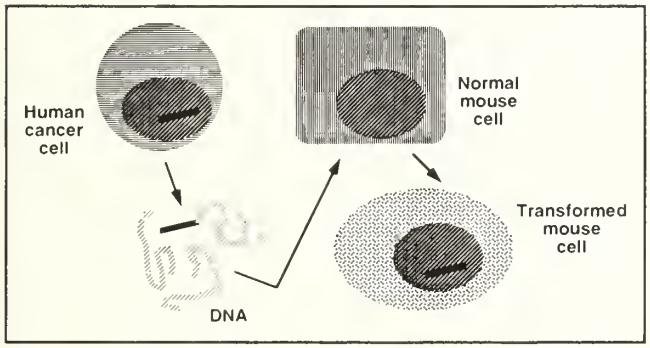

Figure 3.—DNA extracted from some human tumors or tumor cell lines contains genetic information that can transform a normal mouse cell into a tumor cell. That oncogenic information is often the activated form of the *ras* oncogene, a gene that is also transduced by retroviruses. Numerous other dominant oncogenes have been discovered by this gene transfer technique.

In malignant hematopoietic neoplasms, oncogenes are often activated by chromosomal translocation. The first such example was chronic myelogenous leukemia with its characteristic Philadelphia chromosome. In the Philadelphia chromosome, the *abl* oncogene of chromosome 9 is fused to the cellular gene *bcr* on chromosome 22. The result is a protein coded for jointly by *bcr* and *abl* sequences. The ABL protein, known for its leukemogenic potency in the mouse, is a protein kinase. The large BCR-ABL fusion product may also function as a deregulated protein kinase, but it contains additional structural features that suggest other possible growth-promoting activities. In Burkitt's lymphoma, the *myc* oncogene, known for its leukemogenic activity in chickens, mice, and cats, is translocated near an immunoglobulin enhancer and is expressed under the control of this enhancer. This deregulated expression of *myc* must be an important factor in lymphomagenesis because it is seen in all cases of Burkitt's lymphoma. Promyelocytic leukemia is characterized by a reciprocal translocation between chromosomes 15 and 17, resulting in gene fusions at both translocation points (Figure 4). One of these generates a product that consists of the retinoic acid receptor attached to sequences of the *pml* gene, which codes for a transcription factor. The PML–retinoic acid receptor chimera probably exerts highly aberrant transcriptional control. The remissions induced in promyelocytic leukemia by retinoic acid therapy are most likely related to the genetic rearrangement affecting the retinoic acid receptor.

Amplification of oncogenes can indicate advanced tumor development. In neuroblastoma a variant of the *myc* oncogene is amplified in the late stages of tumor development, and in mammary carcinoma the amplification of the *erb* B-2 oncogene, a relative of the epidermal growth factor-receptor gene, is correlated with the disseminated form of this malignant disorder.

The normal growth-regulatory function of cellular oncogenes, the proven tumor-inducing potential of their mutated versions, and the common occurrence of such mutated oncogenes in human tumors all are strong indications of a causal role for oncogenes in human cancer.

Oncogenes Cooperate to Induce Cancer

In some experimental systems, a single oncogene can induce the transformation of a normal cell to a tumor cell; the single gene is necessary and sufficient for the process of oncogenesis. Oncogenes that are transduced by retroviruses, in particular, show this high potency, possibly because they are both overexpressed and mutated structurally. Often, however, a single activated oncogene induces cellular changes that are only partly between normal and tumor cells. Enhanced growth properties may be observed without tumorigenicity. In these situations, two oncogenes with different biochemical functions may complement each other to achieve full transformation. For instance, the activated *ras* oncogene is a poor transformer for normal rat fibroblasts that are freshly explanted from the animal. In conjunction with an activated *myc* oncogene, however, *ras* becomes an efficient transformer. Several such combinations of complementing oncogenes exist, a reminder of the fact that carcinogenesis is a multistep process. In human tumors, too, more than one growth-regulatory gene is changed. The oncogenic phenotype of the cell results from the combination and cooperation of these multiple genetic changes.

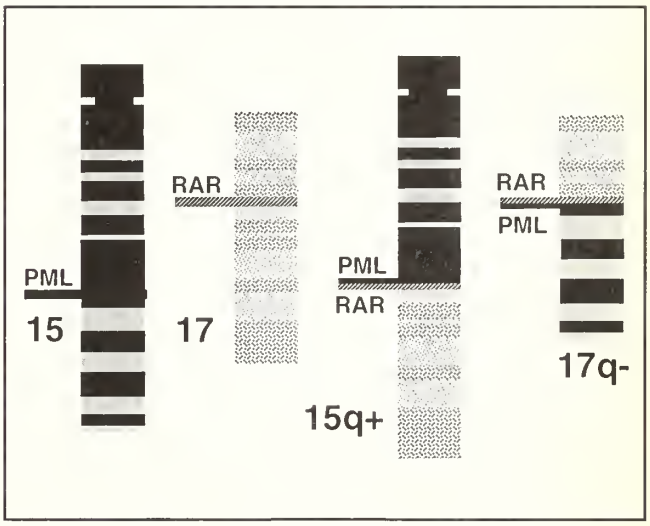

Figure 4.—The translocation between chromosomes 15 and 17 is characteristic of acute promyelocytic leukemia. It results in the fusion of the retinoic acid receptor to a transcription factor, PML. The fusion protein is probably a malfunctioning transcriptional regulator.

Observations on Inherited Cancer Point to the Existence of Tumor Suppressor Genes

In an important experiment performed almost three decades ago, tumor cells were fused with normal cells to produce hybrids that contained the genetic material of both parental cell types. Surprisingly, in some combinations the hybrid cells were nontumorigenic but, on culture and following the loss of chromosomes from the normal parent, tumorigenic variants reappeared in the population (Figure 5). These observations can be explained by postulating the existence of genes in the normal genome that suppress the oncogenic phenotype. Loss of these tumor suppressors allows the reemergence of malignant cellular properties. Initially these experiments did not receive the attention they deserved, in part because they seemed incompatible with the concept of the dominant transforming oncogene, a concept that had

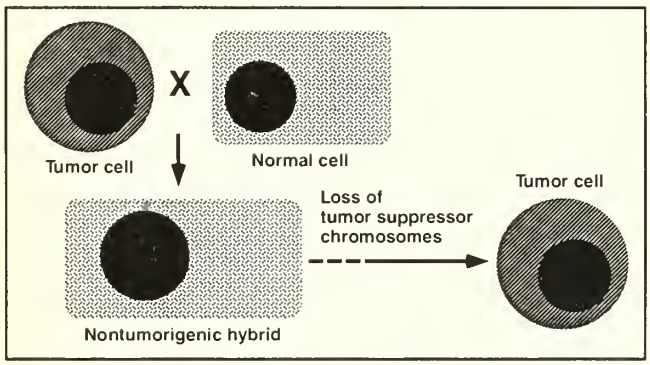

Figure 5.—Fusion of a tumor cell with a normal cell often yields a nontumorigenic hybrid. Loss of chromosomes from the normal parent leads to the reemergence of malignant properties. The lost chromosomes may therefore contain tumor suppressor genes.

gathered strong support from work with tumor viruses. Another line of investigation, however, also led to tumor suppressor genes—the analysis of inherited cancer. The paradigm in this field is retinoblastoma, which occurs as an inherited cancer, often bilaterally, but can also occur sporadically. Genetic epidemiologic studies suggested that two mutations were needed for the development of retinoblastoma (Figure 6). In the inherited form, one of these mutations is transmitted through the germ line, and the second mutation occurs somatically. In the sporadic form of the tumor, both mutations are somatic. Frequent deletions seen in chromosome 13 in retinoblastoma cells defined an initial target area for the

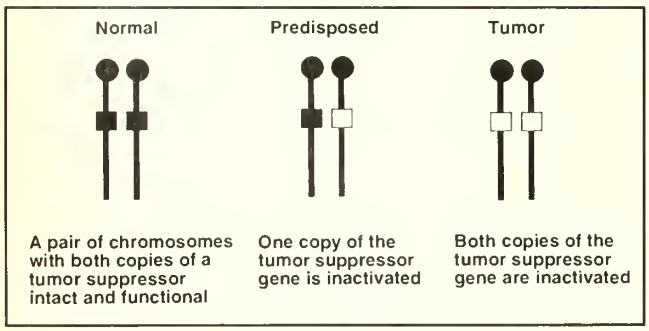

Figure 6.—Retinoblastoma results from two mutations that inactivate both alleles of the same gene, the Rb tumor suppressor. In the inherited form of this disease, one of the inactivating mutations is transmitted through the germ line and the second one occurs during somatic development. In the sporadic form, both Rb mutations are somatic.

study of the causal mutations and led to the discovery that both mutations affect the same gene, inactivating its function. In its active state, the retinoblastoma (Rb) gene codes for a tumor suppressor protein. When both copies of the gene are functionally lost, the resultant lack of growth-attenuating activity causes oncogenic transformation of cells in a specific state of differentiation, such as retinoblasts. The second mutation in the Rb gene can occur by somatic crossover, by nondisjunction followed by duplication of the mutated gene, or by gene conversion—all mechanisms that generate homozygosity in the Rb locus. This homozygosity or loss of heterozygosity of specific chromosomal loci in tumor tissue has become an important signal that marks the location of tumor suppressor genes, both copies of which must be inactivated to abolish the tumor-suppressive effect.

The Rb gene has been cloned. It codes for a protein that is localized in the cell nucleus. If Rb is introduced and overexpressed in tumor cells that lack a functional copy of that gene, the oncogenicity of these cells is substantially reduced or abolished, showing that Rb does have a tumor-suppressive effect in the cell.

Oncoproteins of DNA Tumor Viruses Bind and Inactivate the Rb Protein

Oncogenic DNA viruses include human and animal papillomaviruses, polyomavirus, simian virus 40 (SV40), and adenoviruses. Unlike retroviruses, these DNA viruses transform cells through the action of one or two genuinely viral proteins. The genes coding for these oncoproteins do not occur in normal cellular genomes. They are components of DNA viral genomes indispensable for virus replication. In adenovirus-transformed cells, the oncogenic proteins are referred to as E1A and E1B. In SV40 cells, oncogenicity is controlled by the large T antigen; in papillomavirus-

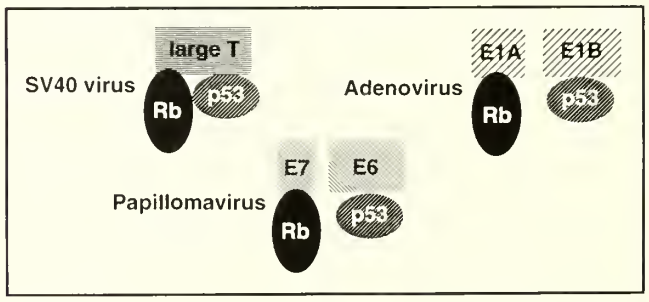

Figure 7.—Three types of DNA virus—simian virus 40 (SV40), adenovirus, and papillomavirus—code for proteins that induce the oncogenic transformation of the cell. These proteins bind to and inactivate the retinoblastoma (Rb) and p53 tumor suppressor proteins. The oncogenicity of these DNA viruses probably derives from this inactivation of Rb and p53.

transformed cells, the oncoproteins are E6 and E7 (Figure 7). Several of these oncoproteins—E1A, large T antigen, and E7—bind the Rb protein; others—E1B, large T antigen, and E6—also bind another cellular tumor suppressor protein, p53, which will be discussed later.

The Rb protein is itself regulated by phosphorylation that varies with the phase of the cell cycle. During the S phase, characterized by active DNA synthesis, the Rb protein is hyperphosphorylated. This highly phosphorylated form lacks the characteristic growth-attenuating properties of the underphosphorylated form that predominates during the quiescent G_1 phase. The oncoproteins of DNA tumor viruses

bind only the active, underphosphorylated form of the Rb protein. Binding to Rb protein takes place in the same regions of the oncoproteins that are needed for transformation. DNA tumor viruses may therefore transform normal cells into cancer cells by coding for proteins that bind and inactivate the tumor suppressor proteins Rb and p53.

Rb Regulates Gene Expression

The interactions of the Rb protein with DNA viral oncoproteins interfere with the physiologic functions of Rb. These functions involve protein-protein binding in normal cells. The active, underphosphorylated Rb protein binds the general transcription factor E2F, thereby inhibiting its activity. In a cell that is transformed by a DNA tumor virus, such as adenovirus, the E1A protein dissociates the union between Rb protein and E2F, allowing E2F to become active when its activity should be reduced by Rb. Thus, Rb controls gene expression through the transcription factor E2F. Interference with this transcriptional regulation can lead to oncogenic transformation of the cell.

Tumor Suppressor p53 Is Often Defective in Human Tumors

The tumor suppressor protein p53 is bound by oncoproteins of DNA tumor viruses. Genetic inactivation of p53 is usually caused by mutation rather than by deletion as in Rb. In cells that lack or have reduced p53 function and consequently are transformed, the normal phenotype can be largely restored by reintroducing and overexpressing a clone of normal p53. The protein is also a transcriptional regulator. It can activate transcription in experimental systems, but this may not be its only function. Mutated forms of p53 that have lost their tumor-suppressive effect no longer stimulate transcription. Mutations that inactivate p53 function are being found in an increasing number of human tumors. Carcinoma of the cervix is a particularly instructive example. Papillomaviruses play a causal role in the genesis of this tumor, and most tumors and tumor cell lines contain papillomaviral genetic material expressing the oncoproteins E6 and E7, which inactivate Rb and p53. Some tumors and tumor cell lines are free of papillomaviruses, however, and probably have a nonviral origin. In these tumors, p53 is genetically mutated and inactive, while in virus-induced tumors p53 is genetically wild type. The end result is the same in both cases: Normal p53 function is eliminated, either phenotypically through combining with a viral oncoprotein or genetically through a disabling mutation. The fact that two different oncogenic mechanisms generate a lesion affecting the function of the same tumor suppressor emphasizes the importance of the suppressor in the regulation of cell growth.

Gene Class	No.	Normal Role	Viral Carcinogenesis	Nonviral Carcinogenesis
Oncogenes	>60	Positive regulator	Carried or activated by retrovirus	Dominant mutations
Tumor suppressor genes	>>7	Negative regulator	Bound and inactivated by viral oncoproteins	Recessive mutations, both copies of the gene inactive in cancer

Figure 8.—Oncogenes and tumor suppressor genes are the yin and yang of growth control. Oncogenes become activated through a gain of function; tumor suppressor genes become oncogenic through a loss of function.

The importance of p53 is also illustrated by the Li-Fraumeni syndrome, a genetic susceptibility to cancer that is characterized by an extraordinarily high familial incidence of tumors at various sites. Carriers in families with the syndrome have an inactivating mutation affecting one copy of the p53 gene, and this mutation is transmitted to offspring through the germ line. The familial tumors show inactivation of p53.

Stage	Mutated Gene	Protein	Type of Regulator	Chromosome
1 *benign*	MCC APC	Transcription factors	Tumor suppressors	5 5
2	ras	Signal transducer	Oncogene	12
3	DCC	Cell adhesion molecule	Tumor suppressor	18
4 *malignant*	p53	Transcription factor	Tumor suppressor	17

Figure 9.—The genetic changes leading to tumorigenesis have been extensively studied in colon carcinoma. Several tumor suppressor genes are lost or inactivated, and at least 1 oncogene is activated.

Cell Malignancy Results From Many Changes in Oncogenes and Tumor Suppressor Genes

The actions of oncogenes and tumor suppressor genes are opposite and complementary (Figure 8). Oncogenes are positive and tumor suppressor genes are negative growth regulators. There are nearly 100 oncogenes known but fewer than 12 tumor suppressor genes. The number of the latter is, however, rapidly increasing. Oncogenes become tumor-inducing agents as a consequence of genetic changes that deregulate their physiologic activity. These changes are typically dominant—a single copy of an activated oncogene in the cell can transform. Normal copies of the oncogene are ineffective in counteracting the oncogenic change. Oncogenes can become activated through the intervention of a retrovirus or by nonviral mechanisms that alter expression levels or coding information. Tumor suppressor genes can exert a growth-regulating effect as single alleles. An oncogenic change usually involves the inactivation of both copies of the gene in the cell. Inactivation of just one copy is a recessive change but can increase the probability of an identical change in the second copy of the gene. Viral interference with the function of tumor suppressor genes occurs at the level of the protein, not the gene. DNA tumor virus oncoproteins bind to and inactivate tumor suppressor proteins. Oncogenes become tumorigenic through a gain of function; tumor suppressor genes acquire oncogenicity through the loss of function.

An instructive example for multiple genetic changes in carcinogenesis is carcinoma of the colon (Figure 9). The development of this tumor proceeds through stages of increasing malignancy starting with benign adenoma and ending with aggressively invasive carcinoma. The acquisition of more and more malignant behavior is accompanied by an accumulation of mutations affecting oncogenes and tumor

suppressor genes. The sequence of these mutations is not fixed; the important feature is the accumulation of multiple genetic changes, each contributing incrementally to the loss of growth control.

Molecular Genetics of Cancer Originated From the Work of Boveri and Rous

Two ideas have dominated the course of cancer research in this century: the idea that cancer results from a genetic change and therefore a cancer cell differs genetically from its normal counterpart, and the idea that viruses can be oncogenic in animals and humans, revealing key mechanisms of oncogenesis. These ideas can be traced back to two seminal figures, Theodor Boveri (1860-1916) and Peyton Rous (1879-1970). Although Rous was Boveri's junior by almost a generation, both did their most important work in the first decade of this century.

Boveri was a professor at the University of Würzburg, Germany. He made fundamental discoveries in chromosome structure and function and in animal development. In a startlingly prescient synthesis of what was then known about genetics and cancer, he proposed in 1902 that cancer was due to chromosomal (genetic) changes. He published his ideas in 1914 in a small volume entitled *Zur Frage der Entstehung maligner Tumoren* (*The Origin of Malignant Tumors*). Today his hypothesis is supported by abundant evidence and provides the theoretical underpinning of virtually all cancer research.

Although Rous did not favor somatic mutation as the basis for cancer, in 1911 he discovered the first oncogenic retrovirus, RSV, one of the most effective somatic mutagens known. Rous was affiliated with the Rockefeller Institute in New York City throughout his scientific career. His pioneering work also extended to DNA tumor viruses, specifically the papillomaviruses. The legacy of Rous therefore includes both oncogenes, revealed by retroviruses, and tumor suppressors, the targets of DNA tumor viruses. He was awarded the Nobel Prize in physiology and medicine in 1966.

By identifying growth-regulatory genes that are altered in cancer, molecular genetics has marked targets for a specific and effective therapy. The recent observation that returning a single tumor suppressor to normal function can abolish the tumorigenicity of a cell with multiple genetic defects is an encouraging sign. The time has come to work on a gene-targeted therapy for cancer.

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Conferences and Reviews

Pathobiology of the Stratum Corneum

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The epidermis is a dynamic system whose metabolic activity is regulated in large part by the integrity of the permeability barrier. This barrier resides in the stratum corneum and comprises a unique 2-compartment system of structural protein-enriched corneocytes embedded in a lipid-enriched intercellular matrix. Lipid extraction or metabolic imbalances, such as essential fatty acid deficiency, produce barrier abnormalities that in turn result in epidermal hyperproliferation, scaling, and inflammation. When the barrier remains intact, lipid imbalances, such as an abnormal cholesterol sulfate:cholesterol ratio in recessive X-linked ichthyosis, can lead to abnormal corneocyte adhesion (visible scale). Both cellular and intercellular proteins also participate in normal desquamation, and protein abnormalities may provoke abnormal scaling (such as filaggrin in ichthyosis vulgaris). Thus, perturbations of the stratum corneum may be the catalyst for a number of skin diseases, rather than the end result of processes that are initiated in subjacent skin layers.

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The major purpose of epidermal differentiation is to generate the stratum corneum, whose primary function is to protect internal organs from desiccation.[1] This purpose is achieved by the exquisite design of the stratum corneum at the cellular and molecular level and by its ability to respond to external injury through an array of metabolic processes. The stratum corneum barrier is formed by the subcellular organization of epidermal proteins and lipids into a two-compartment system with a continuous extracellular lipid matrix surrounding lipid-depleted, protein-enriched cells (corneocytes) (Figure 1). The strategic location of lipids within the cellular interstices and their organization into membrane bilayers imparts impermeability to this tissue. The importance of the barrier is shown most dramatically by the life-threatening consequences of large surface area burns and when it is underdeveloped, as in premature infants with low birth weights. In these and other pathologic conditions, increased transepidermal water loss can lead to dehydration and the entry of pathogenic microbes.

New corneocytes move apically over about 14 days, following which they are shed invisibly (desquamation). Although this precisely controlled process is still poorly understood, lipids, extracellular hydrolytic enzymes, and intercellular junctions (desmosomes) all appear to participate. In pathologic desquamation, the stratum corneum becomes thicker (hyperkeratosis), imparting a "dry" or scaly appearance to the skin. Instead of detaching as single cells, corneocytes are shed in clusters, forming visible scales. In its most severe forms, as in harlequin ichthyosis, the formation of massive platelike scales can interfere with respiratory movements and feeding. Increased stratum corneum thickness occurs from either hyperproliferation, with a more rapid transit of cells through the epidermis that results in an expanded population of incompletely differentiated, cornified cells, or abnormal retention due to a failure of intercellular detachment (normal proliferation rates and transit times).

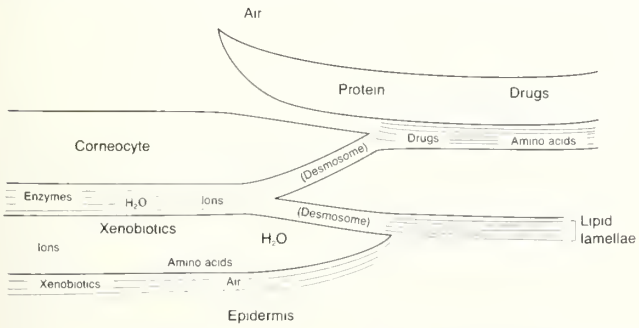

Figure 1.—Lipid-depleted "bricks" (corneocytes) are embedded in a lipid-enriched "mortar" organized into intercellular lamellar bilayers. The intercellular spaces contain pockets of desmosomes, water, ions, and enzymes, plus exogenous drugs and other xenobiotics, resulting in considerable microheterogeneity.

Stratum Corneum Development

Differentiation proceeds as postmitotic keratinocytes migrate apically through the spinous and granular layers, until these cells reach the stratum corneum as enlarged, flattened squames devoid of organelles. As noted, the currently accepted model of the structure of the stratum corneum is of a bicompartmental architecture of protein-aqueous cells (corneocytes) embedded in a continuous lipid-enriched but heterogeneous intercellular matrix (Figure 1).[2] The corneocytes are filled with bundles of keratin filaments synthesized initially in the basal and spinous cell layers. The assembly of keratin filaments into still larger bundles within the corneocyte is aided by matrix proteins synthesized in granular cells that appear initially as distinctive granules (keratohyalin).[3,4] One of these interfilamentous matrix proteins, filaggrin, is histidine-rich and basic. In addition to filaggrin's role in the assembly of keratin bundles during terminal differentiation, its hydrolysis is carefully regulated to generate free amino acids that contribute to the water-holding properties of the stratum corneum.[5,6] The conversion of filaggrin to amino acids is preceded by the dephosphorylation of a large

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precursor molecule (profilaggrin) that is then susceptible to proteolytic degradation into lower-molecular-weight polypeptides.[6] Corneocytes also have a characteristic envelope produced by the cross-linking of precursor proteins such as involucrin[7] and loricrin[8] and by the calcium-activated enzyme, transglutaminase,[7] which imparts increasing rigidity to corneocytes during stratum corneum transit.[9] Individual corneocytes interdigitate along their lateral margins and are further bound together by protein- and glycoprotein-enriched bridging molecules called desmosomes, which slowly disintegrate during transit from the inner to the outer layers of the stratum corneum.[10]

The lipid enrichment of the stratum corneum interstices results from the intercellular deposition of epidermal lamellar body contents (Figure 2).[2,11-15] Lamellar bodies measure

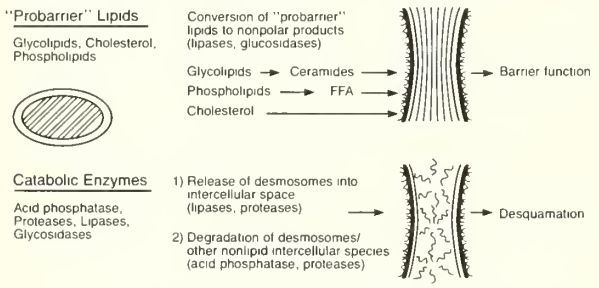

Figure 2.—This speculative diagram links available information about lamellar body lipid and hydrolase content to modulations leading to barrier formation and desquamation. The release of desmosomes may be aided by the detergent action of free fatty acids (FFA), or phospholipases or proteases (or both) at sites of desmosomal insertion (from Elias[15]).

0.2 to 0.3 μm in diameter and are ovoid, secretory organelles synthesized within the spinous and granular cell layers that secrete their contents into the intercellular spaces at the base of the stratum corneum.[13,14] These distinctive organelles are enriched in glycosphingolipids, phospholipids, cholesterol, and an array of hydrolases (Figure 2).[2,16-18] Stratum corneum lipids are virtually devoid of phospholipids and are selectively enriched in sphingolipids (ceramides), free sterols, and free fatty acids, with lesser quantities of nonpolar lipids and cholesterol sulfate.[2,13,19] Ceramides, in particular, have been pinpointed as critical ingredients of the barrier (Table 1; also discussed later). Among the organelles' catabolic enzymes are lipid hydrolases and glycosidases that catalyze the transformation of glycosphingolipids and phospholipids to ceramides and free fatty acids, respectively. The cholesterol pool is not metabolized and is apparently expanded by the degradation of cholesterol sulfate to cholesterol by steroid sulfatase.[20,21]

Lamellar body lipids appear to be compressed within the interior of the organelle ("pleated sheets"), and immediately after secretion these sheets begin to unfurl (elongate) in the intercellular spaces.[13,22] As a result of the codeposited hydrolytic enzymes,[23,24] the unfurled sheets initially form more elongated sheets that transform into the basic lamellar unit structure in the mid-stratum corneum.[22] These modulations in protein and lipid composition and architecture indicate ongoing biochemical processes, implying that the stratum corneum is not inert but in fact possesses limited metabolic activity.

Epidermal Lipid Synthesis

As in other tissues, epidermal lipid synthesis is charged not only with producing lamellar body lipid contents,[25] but also with providing lipid for new membranes for dividing and expanding cells. Although a small contribution of lipid is derived from dietary sources such as essential fatty acids, systemic delivery to the skin is minimal.[26] In contrast, the epidermis synthesizes at least one critical lipid for export, cholecalciferol or vitamin D_3.[27] The ability of the epidermis to synthesize cholesterol, sphingolipids, and fatty acids for the stratum corneum barrier has been demonstrated in several ways. First, the incubation of epidermis (separated from dermis) under organ culture conditions results in the incorporation of radiolabeled precursors into stratum corneum lipids.[28-30] Second, the epidermis contains extraordinarily high levels of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase[31] and serine palmitoyl transferase activities,[32] the key regulatory enzymes of cholesterol and sphingolipid synthesis, respectively. Third, the messenger RNA (mRNA) for HMG-CoA reductase has recently been isolated from the epidermis.[33] Fourth, disruption of the epidermal permeability barrier by either polar organic solvents, tape stripping, or dietary restriction of the essential fatty acid, linoleic acid, resulting in essential fatty acid deficiency, leads to accelerated epidermal cholesterol, ceramide, and fatty acid synthesis.[32,34-36] Moreover, the activity, mass, and mRNA levels of HMG-CoA reductase and the activity of serine palmitoyl transferase change in parallel with barrier disruption.[31-33] In addition, if after barrier disruption the barrier is artificially restored by covering the skin with a water vapor-impermeable wrap, then both lipid synthesis and enzyme activity return to normal levels[31,37]—no stimulation occurs. Finally, topical applications of inhibitors of either HMG-CoA reductase[38] or serine palmitoyl transferase[39] immediately after barrier disruption lead to a reduction in epidermal cholesterol and sphingolipid synthesis, respectively, and a corresponding delay in barrier repair. Thus, maintaining the barrier to water loss is a key factor in the regulation of epidermal lipid synthesis.

Relationship of Barrier Function to Epidermal DNA Synthesis

Although it is generally assumed that epidermal DNA synthesis is regulated by requirements for cell replacement because of desquamation or cellular injury—mass balance considerations—recent studies suggest that barrier function is an important regulator of this process.[40] For example, barrier disruption by organic solvent treatment, tape stripping, or essential fatty acid deficiency increases epidermal DNA synthesis, and the extent of stimulation is proportional

TABLE 1.—*Evidence for Importance of Sphingolipids in Barrier Function*

Barrier disruption by organic solvents requires application of solvents that extract sphingolipids
Stratum corneum water retention is improved by addition of ceramides to damaged skin
Sphingolipids are enriched in long-chain, saturated *N*-acyl fatty acids (C24:0, C26:0) that are hydrophobic and ideal for preventing excess water loss
When barrier requirements are less exacting (as in marine mammals), the long-chain, saturated *N*-acyl species of sphingolipids are replaced by shorter-chain species
Epidermal sphingolipids are enriched in the essential fatty acid, linoleate (C18:2), which is replaced by oleate (C18:1) in essential fatty acid deficiency, concomitant with barrier disruption

to the degree of barrier abrogation. Furthermore, as with epidermal lipid synthesis, occlusion with a water vapor-impermeable wrap largely blocks the expected burst in DNA synthesis. Finally, the topical administration of linoleic acid and occlusion repair the barrier defect and normalize DNA synthesis in fatty acid-deficient epidermis. In contrast to the increase in lipid and DNA synthesis, barrier function does not stimulate bulk protein synthesis,[40,41] and topical applications of inhibitors of protein synthesis (cycloheximide and puromycin) do not delay the initial stages of barrier repair.[41] Because many skin disorders, such as psoriasis, all of the eczemas, and some forms of ichthyosis, display both abnormal barrier function and epidermal hyperplasia, it is tempting to speculate that a primary abnormality in barrier function could initiate not only the epidermal hyperplasia but also the subsequent inflammatory features of these disorders. In fact, cytokine signals have been identified recently that could initiate this cascade.[42]

Pathobiology of the Stratum Corneum

Lipid Abnormalities in the Stratum Corneum

Acute loss of lipid from the stratum corneum. As noted earlier, the main function of stratum corneum lipids is to form the permeability barrier, and a primary result of barrier damage is an increase in transepidermal water loss. Although lipids can be extracted from the stratum corneum in the laboratory by topically applying organic solvents or detergents,[43] they also can be extracted through both occupational and recreational pursuits. Whereas the extraction of more nonpolar lipids causes only minor barrier damage, extraction of more polar lipids (ceramides and cholesterol) causes profound barrier damage.[44] Although these studies demonstrate again the importance of polar lipids for barrier function (see also Table 1),[2,32,45,46] they do not exclude a combined, cooperative role for all of the major lipid species such as ceramides, cholesterol, and free fatty acids. Barrier disruption not only removes lipids but also allows a simultaneous, passive loss of extracellular calcium and potassium ions.[47] These ions inhibit the secretion of preformed lamellar bodies into the intercellular spaces and the onset of new lipid synthesis under basal conditions.[48,49] Thus, the rapid restoration of barrier function can be attributed to the stimulation of lipid synthesis and lamellar body secretion as a consequence of ion depletion.[48,49]

In contrast, chronic assaults on the barrier as with repeated applications of detergents[50] or the administration of a diet deficient in essential fatty acids[51] produce not only lipid depletion but also increased scaling and roughness, in part attributable to epidermal hyperplasia.[51,52] As noted, barrier disruption immediately generates cytokines,[42] which could trigger epidermal hyperplasia. Moreover, on reaching the dermis, these cytokines might also initiate dermal inflammation. Whatever the exact mechanism, epidermal hyperplasia also results in abnormal desquamation, possibly through the arrival of incompletely differentiated cells in the stratum corneum. Such cells may contain immature lamellar bodies, which may lack the appropriate complement of lipids or hydrolytic enzymes.[16-18] The outcome, in any case, is a stratum corneum comprising both abnormal lipids and proteins with poor barrier function and impaired desquamation.

Essential fatty acid deficiency. Abnormal skin function results from the removal of the essential fatty acid, linoleic acid (ω6,C18:2), from the diet.[51] The skin is a major target in essential fatty acid deficiency, with increased transepidermal water loss, scaling, and alopecia as cardinal features. This deficiency can occur in patients undergoing prolonged lipid-free parenteral nutrition and in nutritionally deprived infants.[53] Cutaneous symptoms of essential fatty acid deficiency develop in rodents after two to three months of the restricted diet. Ultrastructural studies have shown that the internal structure of the lamellar body is disturbed[54] and that lipid bilayers are absent or defective in the stratum corneum intercellular spaces,[55,56] allowing the passage of excess water into the environment. Although linoleic acid is found among all epidermal acyl lipids, it is concentrated in acylsphingolipids (50% to 75% of esterified fatty acids),[57-59] where it is esterified to the ω-terminus of a novel, long-chain (C30 to C34) α-hydroxy monounsaturated fatty acid. The exceptionally long hydrocarbon chains of these molecules may determine the arrangement of the lipid bilayers in lamellar bodies or the stratum corneum intercellular spaces.[58] The molecular basis of this deficiency is thought to be the replacement of linoleic acid by oleic acid in these molecules,[60] with a subsequent defect in bilayer function leading to excess water loss.

As noted earlier, the barrier defect in essential fatty acid deficiency also is accompanied by epidermal hyperplasia, and both are reversed by dietary or topical replenishment with linoleic acid.[40,61] Because topical columbinic acid, which undergoes limited metabolism by cyclooxygenase or lipoxygenase pathways, or linoleic acid in the presence of inhibitors of the cyclooxygenase and lipoxygenase pathways both correct the barrier abnormality,[40,62] the barrier defect presumably results from the deficiency of linoleic acid itself, rather than the lack of a cyclooxygenase or lipoxygenase metabolite. Finally, perturbations in essential fatty acid metabolism have been invoked in the pathogenesis of several other skin diseases, including acrodermatitis enteropathica, acne, atopic dermatitis, and keratosis follicularis (Darier's disease).[63]

Drug-induced lipid abnormalities. Certain hypocholesterolemic drugs—nicotinic acid, triparanol—which inhibit the distal steps of cholesterol synthesis, induce abnormal desquamation (Table 2).[64-67] Surprisingly, lovastatin (formerly called mevinolin) and its relatives, which inhibit more proximal steps of cholesterol synthesis—that is, at HMG-CoA reductase[68]—do not cause cutaneous side effects.[69,70] Possible explanations include a compensatory mechanism employed by the epidermis (discussed later) or significant first-pass hepatic clearance.[70]

Another hypocholesterolemic agent, azacosterol hydrochloride, produces palmoplantar keratoderma in humans and generalized hyperkeratosis in rodents.[71,72] The stratum corneum lipids show a substantial decrease in free sterol content,[71] with enrichment in sphingolipids,[71-73] an alteration that may be sufficient to disrupt the lipid bilayer organization in the interstices of the stratum corneum, resulting not only in abnormal desquamation but also increased transepidermal water loss and epidermal hyperplasia.[72-74]

Although lovastatin produces no cutaneous side effects when administered parenterally, a single topical application to hairless mice causes profound inhibition of epidermal cholesterol synthesis,[38] with increased transepidermal water loss, scaling, and hyperplasia occurring after five to seven daily topical applications.[75] Lamellar bodies appear abnormal in size and internal structure, and these abnormal contents are transferred to the intercellular spaces of the stratum

TABLE 2.—*Drugs That Produce Both Hypocholesterolemia and Ichthyosis*

Drug (Code Designation or Chemical Name)	*Therapeutic Use*	*Cutaneous Effects*
Nicotinic acid	Hypocholesterolemic agent	Generalized dry skin
Triparanol (MER-29)	Hypocholesterolemic agent	Ichthyosis
Azacosterol HCl (20,25-diazacholesterol)	Hypocholesterolemic agent	Palmoplantar keratoderma
Gemfibrozil	Hypocholesterolemic agent	Exacerbation of psoriasis
Butyrophenone (WY-3457)	Antipsychotic agent	Ichthyosis
Pipamperone/butyrophenone	Antipsychotic agent	Palmoplantar keratoderma
Dixyrazine/phenothiazine	Major tranquilizer	Ichthyosis

HCl = hydrochloride

corneum. Yet, the lipid content of the stratum corneum shows normal cholesterol levels with an increased content of free fatty acids. A compensatory increase in new enzyme synthesis results in a return to normal cholesterol biosynthesis, but the concomitant increase in fatty acid biosynthesis (>250% of control) persists, altering the sterol:free fatty acid ratio of the stratum corneum lipids and again causing membrane abnormalities, increased water loss, and epidermal hyperplasia.

Lipid abnormalities associated with genetically determined disorders. It has been known since 1978 that a deficiency of the microsomal enzyme, steroid sulfatase,[76-78] is the cause of the inherited disorder, recessive X-linked ichthyosis. This enzyme is membrane-bound and hydrolyzes both 3-β-sulfate esters of cholesterol and the sulfated steroid hormones. The most constant phenotypic characteristic of recessive X-linked ichthyosis is generalized hyperkeratosis (ichthyosis). Although the absence of acanthosis and a near-normal tritium-thymidine labeling index indicate that the hyperkeratosis is caused primarily by delayed desquamation rather than hyperproliferation,[79,80] rates of transepidermal water loss are slightly increased over normal.[81]

Scale lipid analysis in recessive X-linked ichthyosis typically reveals a fivefold increase in cholesterol sulfate and a 50% decrease in free-sterol content.[82] Because the proportion of cholesterol sulfate is lower in the outer stratum corneum than in whole or inner stratum corneum sheets,[21,83] ongoing hydrolysis of cholesterol sulfate by steroid sulfatase during stratum corneum transit may be critical for normal desquamation.[20,21] For example, cholesterol sulfate causes an aggregation of synthetic lipid membranes[84]; hence, desquamation may require destabilization of membrane bilayers. Alternatively, excess cholesterol sulfate could alter the "solid-liquid" phase transition temperature of intercellular lipid mixtures (desquamation may require lipids in the "liquid" state)[85]; or cholesterol sulfate, in conjunction with calcium ions, may mediate the binding of adjacent cells due to its negative charge (normal desquamation then would require the release of such cell-cell interactions).[86]

Although topically applied cholesterol sulfate induces scaling in hairless mice, topical cholesterol reduces the scaling abnormality in recessive X-linked ichthyosis.[20,87] Thus, abnormal scaling could be caused by reduced sterol content, as in the drug-induced syndromes discussed earlier. Moreover, because cholesterol sulfate inhibits cholesterol synthesis in both cultured fibroblasts and keratinocytes by inhibiting HMG-CoA reductase,[87,88] it could be a physiologic feedback regulator of epidermal sterologenesis. Thus, many mechanisms can be invoked as the cause of the hyperkeratosis in this disorder.

Refsum disease is an autosomal recessive scaling disorder associated with neurologic abnormalities.[90-92] Abnormal accumulations of the plant-derived, branched-chain fatty acid, phytanic acid (3,7,11,15-tetramethylhexadecanoate), occur in target tissues,[93,94] and scaling abates with the dietary restriction of phytanic acid intake.[95] Epidermal lipid analysis shows a massive substitution of phytanic acid for other long-chain fatty acids in all esterified species.[90] Although it has been postulated that substituting phytanic acid for *N*-acyl fatty acids in stratum corneum acylsphingolipids could lead to altered stratum corneum membrane bilayers,[60] these species appear to be normal in Refsum disease.[96]

Ichthyosis is also a striking characteristic of the autosomal recessive disorder, Sjögren-Larsson syndrome,[97,98] which results from deficiency of the enzyme fatty alcohol oxidoreductase, leading to the accumulation of fatty alcohols (or a reduction of free fatty acids).[99,100] Although the link between fatty alcohol oxidoreductase deficiency, epidermal lipid content, and the scaling disorder has yet to be defined, the ichthyosis is at least in part due to hyperproliferation.[101]

Ichthyosis and myopathy are the most consistent clinical features of neutral lipid storage disease, an autosomal recessive disorder characterized by the widespread tissue storage of triacylglycerol within non–membrane-bound cytoplasmic droplets.[102] Although the precise metabolic defect remains undefined, metabolic studies point to a defect in intracellular triacylglycerol lipolysis.[103-105] Lipid storage is evident in basal and spinous cell keratinocytes and in other cell types in the skin.[106] In the granular cell layer, the number of lamellar bodies is increased and their contents are distended by electron-lucent material, which may represent droplets of triacylglycerol. These droplets coalesce and displace the lamellar bilayers after secretion into the intercellular spaces. Yet, the scales in neutral lipid storage disease unexpectedly showed normal amounts of triacylglycerol and free fatty acids, leaving the nature of the lipid abnormality leading to abnormal desquamation in this disorder as yet unknown.

Although the scales from patients with disorders of cornification, such as congenital ichthyosiform erythroderma, often contain large quantities of *N*-alkanes (as much as 45% of scale lipids), recent studies have shown that these substances are of exogenous origin.[107,108] Electron-microscopic studies of stratum corneum of patients with this disorder revealed a spectrum of abnormalities, including desmosomal persistence, unusual membranous inclusions,[109] lipid phase separation, disorganization of lipid lamellae, and distorted lamellar bodies.[110] Both the secretion of lamellar bodies and the complement of hydrolytic enzymes appear to be deficient in congenital ichthyosiform erythroderma,[111] and an abnormal delivery of lamellar body-derived enzymes could result in one or more of the abnormalities described. Because increased transepidermal water loss and hyperproliferation are

also features of this disorder, the membrane abnormalities again could be linked to the dermatosis, as in essential fatty acid deficiency.

Several investigators have observed lipid vacuoles, unusual membrane structures, and an absence of normal lamellar bodies in harlequin ichthyosis,[112-114] an autosomal recessive disorder of unknown cause, characterized at birth by massive platelike scales and often early death. It appears that a defect in lamellar body formation results in an absence or paucity of intercellular membrane bilayers in the stratum corneum, with abnormal barrier function and hyperplasia again as one result. The failure of lamellar body formation, however, also would result in a lack of hydrolytic enzyme delivery to the interstices, contributing to the abnormal desquamation.

Protein Abnormalities in the Epidermis

Keratins. Despite the ubiquitous nature of keratin molecules, the only known genetic defect in keratin synthesis produces blistering in the viable epidermis,[115] rather than abnormal desquamation.

Desmosomes. Desmosomes have been implicated in the pathogenesis of many skin conditions, including psoriasis, Refsum disease, harlequin ichthyosis, X-linked ichthyosis, and ichthyosis vulgaris.[111] In normal skin, desmosomes are present throughout the epidermis but undergo progressive degradation within the stratum corneum.[10] In the lower layers they are distributed along the whole length of the cell, but desmosomes disappear in the middle and upper layers of the stratum corneum.[10] It is thought that enzymatic degradation, possibly by glycosidases[116] and proteases,[117] removes desmosomes and that their progressive degradation is one factor that enables cells to be shed invisibly from the surface of the skin. Presumably the desmosome-degrading enzymes are delivered to the intercellular spaces by the secretion of lamellar bodies, which are known to contain a variety of catabolic enzymes, including proteases and glycosidases.[16,18] Differential rates of desmosomal degradation may be due to protective glucose molecules,[116] the presence of enzyme-resistant proteins, or factors in the microenvironment, such as protease inhibitors or lipid annuli, that may alter the susceptibility of desmosomes to degradation.[10,116] For example, certain proteases are inhibited by cholesterol sulfate, which suggests yet another role for this lipid in normal and pathologic desquamation (discussed later).

In psoriasis, the number of desmosomes remains high throughout the stratum corneum,[118,119] a finding that could result from one or more of the abnormalities postulated earlier. Electron-microscopic studies also have shown that the lamellar bodies of psoriatic epidermis are morphologically abnormal,[120] and they perhaps lack the normal complement of either lipids or enzymes. This observation could again explain the increase in transepidermal water loss in psoriasis[120] that in turn could provoke the epidermal hyperplasia.[40]

There is also an abnormal persistence of desmosomes into the outermost layers of stratum corneum in recessive X-linked ichthyosis.[121-123] As noted earlier, the increased levels of cholesterol sulfate in the stratum corneum of patients with this disorder may contribute to desmosomal retention,[82] particularly if this molecule functions as a protease inhibitor in epidermis, as it does in sperm, where it inhibits acrosin, a protease involved in capacitation.[124] Thus, the abnormal persistence of cholesterol sulfate could prevent the proteolysis of desmosomes and account for the abnormal desquamation.

Desmosomal structures also reportedly persist into the outer stratum corneum layers in Refsum disease and in harlequin ichthyosis.[92] Furthermore, the thickened stratum corneum that develops on the hands and feet as a result of repeated but mild friction,[125] a process that when exaggerated can lead to calluses or corns, displays a similar desmosomal abnormality.[125] In each of these cases, the persistence of desmosomes into the outer layers of the stratum corneum can be attributed to defective lamellar body protease delivery, which in turn could account for the abnormality in desquamation.

Profilaggrin and filaggrin. A disturbance in the degradation of profilaggrin, the principal component of keratohyalin granules, may be responsible for a variety of stratum corneum abnormalities. As noted earlier, proteolysis occurs within the stratum corneum, liberating hygroscopic free amino acids.[6] A blockade of this sequence leads to a build-up of filaggrin and a paucity of amino acids in the stratum corneum.[5,126] Without these molecules, the amount of water retained in the stratum corneum is decreased. Because water has a profound effect on the plasticity and elasticity of the stratum corneum, its absence is associated with inflexibility, cracking, scaling, and flaking of the skin. Furthermore, water uptake by the stratum corneum exerts mechanical stresses as the corneocytes swell, which, in combination with weakened intercellular cohesive forces, may aid desquamation. Ichthyosis vulgaris appears to arise from a genetic defect in the regulation of profilaggrin synthesis.[127] Thus, ichthyosis vulgaris represents a retention type of hyperkeratosis, and it has been hypothesized that reduced filaggrin content results in insufficient quantities of osmotically active materials in the stratum corneum,[128] with insufficient swelling required for normal desquamation. Likewise, in harlequin ichthyosis, profilaggrin is either absent or, if present, not processed normally to filaggrin.[129] It appears unlikely, however, that this mechanism alone could account for the massive platelike scales of this condition, since lipid abnormalities also are present.[112,113]

Cornified envelopes. The cornified envelopes of the stratum corneum cells have been examined in various pathologic skin conditions associated with congenital disorders of cornification.[9] Whereas the morphologic features of isolated cornified envelopes in parapsoriasis, the keratitis-ichthyosis-deafness syndrome, palmoplantar keratoderma, pachyonychia congenita, and erythrokeratoderma variabilis all appear normal, in keratosis follicularis, the ichthyosis-brittle hair syndrome, ichthyosis vulgaris, and psoriasis, the number of fragile-appearing cornified envelopes appears to be increased.[9] Although these changes may affect the tensile strength of the stratum corneum, they are less likely to result in increased transepidermal water loss. If abnormalities of the cornified envelope were to influence the organization of intercellular lipids into lamellar bilayers in these domains, then profound alterations in barrier function or desquamation might occur.

Conclusion

The stratum corneum, the outermost protective layer of the skin, is the end product of epidermal differentiation and involves many biochemical processes. Awareness of the structural and biochemical complexity of this tissue is replacing old views of the stratum corneum as dead or inert. The same dynamic events that form the functional stratum cor-

neum also expose it to pathologic processes, including abnormal barrier function, deranged desquamation, and hyperproliferation. Abnormalities in lipid composition and, to a lesser extent, protein composition are linked to stratum corneum pathophysiology. Alterations in stratum corneum lipid composition are associated with perturbations of both barrier function, resulting in increased transepidermal water loss, and desquamation, resulting in a thickened, scaly stratum corneum. Deranged desquamation is also associated with protein abnormalities, particularly the persistence of desmosomes into the outer layers of the stratum corneum. Perturbed barrier function, abnormal desquamation, and hyperproliferation appear to be intimately linked and can be either the cause or the consequence of the others. Pathobiologic conditions of the stratum corneum invariably show one, two, or all three of these characteristics.

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Long-Range Safety and Protective Benefits of Angiotensin-Converting Enzyme Inhibitors for Hypertension

Do We Need More Clinical Trials?

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Discussants
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This is an edited summary of an Interdepartmental Dean's Conference arranged by the Department of Medicine of the University of California, Davis, School of Medicine and Department of Veterans Affairs, Martinez Medical Center, Martinez, California. The permanent chair and organizer of these conferences is Michael C. Geokas, MD, PhD, Professor of Medicine and Biological Chemistry (Emeritus).

Inhibition of the renin-angiotensin system is being applied with considerable success to the treatment of hypertension and heart failure. Angiotensin-converting enzyme (ACE) inhibitors are the only currently available agents that can achieve this objective. In general, the major therapeutic effects of these agents in the treatment of mild to moderate hypertension or of heart failure are exerted on the vascular tissue through inhibition of the renin-angiotensin system and, secondarily, of the sympathetic nervous system. When cardiovascular functional reserve is diminished and autoregulation of regional and systemic blood flow is strained, however, ACE inhibitors may affect other organ functions (heart, kidneys, and possibly brain), hormones other than the renin system, and local tissue humoral systems. The interrelations between the renin-angiotensin system and several other vasoactive systems—including circulating and locally generated tissue hormones and centrally acting neurohormonal factors—are complex and unclear. A better understanding of these mechanisms and interrelations would allow for a more rational therapeutic use of these agents. Unknown also are the clinical effects of prolonged ACE inhibition. Whether the use of ACE inhibitors can provide primary cardiorenal protection requires proof through definitive clinical trials.

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MOHINDER P. SAMBHI, MD, PhD*: The introduction of angiotensin-converting enzyme (ACE) inhibitors as new therapeutic tools for hypertension and for heart failure has, in many ways, revolutionized the treatment of these cardiovascular disorders. Certain fundamentally important questions, however, remain. Do we know all we need to know about the mode of action of these drugs? Can they protect against long-term cardiovascular-renal damage, as has been claimed?[1] Or do we need future well-designed and well-controlled clinical trials—despite their inherent limitations—to answer these crucial questions? In this rapidly evolving area, the present discussion cannot provide unequivocal or comprehensive answers, but it does provide a perspective from clinical investigators who have directed their attention over the years to this research area.

Elucidating the precise mode of action of ACE inhibitors promises to fill in some gaps in our knowledge of the pathophysiology of hypertension and of heart failure. More specifically, such knowledge might clarify the functional importance of the endocrine actions (circulating angiotensin II) versus the paracrine and autocrine actions (effects on neighboring and same cells of locally produced angiotensin II) of the renin-angiotensin system in health and disease. The development of therapeutic tools—better ACE inhibitors, specific inhibitors of the enzyme renin, or specific receptor antagonists for angiotensin—derives its impetus from the same rationale. Angiotensin-converting enzyme inhibitors lower blood pressure in hypertension or lower afterload in heart failure predominantly by inhibiting angiotensin activity and, secondarily, sympathetic nervous activity. It is not clear, however, in which organs and tissues this inhibition is of greatest importance.

When ACE (kininase II) activity is suppressed, vasoactive kinins accumulate and may mediate certain metabolic consequences, such as improved insulin sensitivity.[2] In animals, the local vasodilatory actions of kinins may contribute to the antihypertensive potential of ACE inhibitors,[3] but this has not as yet been shown to pertain in the clinical use of these agents.

Angiotensin can be produced locally in several tissues.[4] Tissue renin-angiotensin systems, controlled independently of the circulatory system, may exist. For example, measurable amounts of essential components of the system are found

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ABBREVIATIONS USED IN TEXT

ACE = angiotensin-converting enzyme
HAPPHY = Heart Attack Primary Prevention in Hypertensives
HDFP = Hypertension Detection and Follow-up Program
IPPPSH = International Prospective Primary Prevention Study in Hypertension
MAPHY = Metaprolol Atherosclerosis Prevention in Hypertension
MRFIT = Multiple Risk Factor Intervention Trial
VA = Department of Veterans Affairs

in tissues, as well as constitutive gene expression of system proteins.[4] This evidence for functionally distinct renin systems in different tissues remains largely circumstantial, however.

Does angiotensin have a normal paracrine or autocrine function—as distinguished from its endocrine function—in various tissues? Such a putative role has not been established for normal or for pathologic states. The endocrine effects of circulating angiotensin II can be measured readily in the whole organism, but the possible tissue-specific paracrine and autocrine effects of locally produced angiotensin II would be selective for the individual organ systems. In cardiac tissue an enzymatic pathway, independent of ACE activity, is capable of generating angiotensin II. Angiotensin-converting enzyme inhibits peripheral resistance by suppressing angiotensin activity in vascular tissue, but it may not substantially affect angiotensin formation in cardiac tissue.[5] Thus, despite ACE inhibition, a failing heart may benefit from the possible inotropic actions of undiminished, or even increased, locally produced angiotensin, compensatory to afterload reduction.[6]

It can be predicted that inhibiting ACE production may be beneficial if the renin-angiotensin system is overactive. Conversely, inhibiting ACE production may be deleterious if a compensating, protective function is being performed by the renin-angiotensin system. For example, in bilateral renal artery stenosis, autoregulation of the glomerular filtration rate and renal blood flow depends entirely on the availability of intrarenal angiotensin. If ACE activity is inhibited, therefore, renal function will be impaired. How do ACE inhibitors affect patients with normal or low renin levels? Angiotensin contributes to the physiologic regulation of blood flow and of organ perfusion as one part of an integrated functional reserve for homeostasis. These overall homeostatic mechanisms can break down and adversely affect the use of ACE inhibitors. For example, if there is severe sodium depletion or volume contraction, inhibiting ACE may result in dangerous hypotension. It is not known whether prolonged ACE inhibition may be deleterious from a deficiency either of the angiotensin generated locally in the tissue renin-angiotensin system or that produced in the circulation.

Is the considerably higher cost of newer ACE inhibitors justified? Can we use cheaper drugs without impairing the long-term cardiovascular and renal protective effects claimed for ACE inhibitors? Industry should assume the major responsibility for funding clinical trials to answer these highly relevant questions.

Mode of Action

HARALAMBOS GAVRAS, MD*: Angiotensin-converting enzyme inhibition is now widely accepted as a first-line approach to treating hypertension and congestive cardiac failure. Numerous experimental and clinical studies of hemodynamic, hormonal, and metabolic effects of various ACE inhibitors conclusively show the advantages of this treatment over other pharmacologic therapies in safety, tolerability, cardioprotection, and patient convenience. Yet, despite more than two decades of intensive research, the exact mode of action of ACE inhibitors remains incompletely understood. In this section I review the mechanisms by which ACE inhibitors are thought to lower the blood pressure.

The era of ACE inhibition started when Ferreira discovered in the venom of a Brazilian snake (*Bothrops jaracaca*) a series of polypeptides that potentiated the effects of bradykinin by inhibiting its enzymatic degradation, hence named bradykinin-potentiating factors.[7] Shortly thereafter, it was discovered that the enzyme that converts angiotensin I to angiotensin II is identical to the kinase II that metabolizes bradykinin.[8] Therefore, ACE inhibition should theoretically interrupt the formation of the vasoconstrictor angiotensin II and lead to an accumulation of the vasodilator bradykinin; both actions should relax blood vessels and reduce blood pressure. As anticipated, when these polypeptides were administered to animals with experimental renovascular hypertension (which is typically angiotensin-dependent) blood pressures fell.[9]

When the first synthetic ACE inhibitor suitable for human use, teprotide, was given intravenously, plasma ACE activity was virtually eliminated within minutes. As a result, angiotensin II was notably suppressed as was plasma aldosterone, whose secretion depends in part on stimulation by angiotensin II of the adrenal zona glomerulosa. Patients with renin-dependent hypertension, such as those with renovascular or malignant hypertension, had a considerably greater decrease in blood pressure than did patients with low-renin essential hypertension.[10] Suppression of aldosterone secretion in high renin states should also contribute to lowering blood pressure by diminishing renal tubular reabsorption of sodium and thus attenuating the vasopressor consequences of excessive sodium retention.

Subsequent short- and long-term studies with the oral ACE inhibitor captopril[11-14] permitted a better evaluation of its hormonal effects. In short-term studies, plasma ACE activity was suppressed after each dose but returned to baseline within about two hours, even though blood-pressure lowering was maintained for six to eight hours. Moreover, after a few days or weeks of ACE inhibition, circulating levels of plasma angiotensin II and aldosterone tended to rise toward baseline, even though antihypertensive action was sustained. More important, in the first few patients, this action did not correlate with baseline renin levels. Subsequently, in large groups of patients, the weak correlation between pretreatment levels of plasma renin activity (a reflection of circulating angiotensin II and an index of the degree of angiotensin II dependency of a given blood pressure level) and the magnitude of blood pressure fall after ACE inhibition became statistically significant, but individual variability resulted in frequent overlap. Indeed, some patients with low-renin hypertension showed a substantial antihypertensive response that tended to be further accentuated with time. It became clear that baseline levels of plasma renin activity could not fully predict a patient's response to the drug.

Why does this dichotomy exist? Some investigators postulated that ACE inhibition affected not only circulating an-

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giotensin II levels but also local angiotensin II generation within the vascular wall. Components of the renin-angiotensin system are known to exist in various tissues, including the vessel wall and the brain,[15-17] and may play an important role in cardiovascular homeostasis. Inhibiting ACE, however, fails to decrease blood pressure in nephrectomized animals. Additional hypotensive mechanisms are clearly involved.

In a comparative study, teprotide was found to have a greater hypotensive action than did another angiotensin II antagonist, saralasin.[18] A partial agonistic activity of saralasin might explain some of this difference. Captopril, however, was found to elicit a considerable antihypertensive response even in patients whose blood pressure failed to decrease despite a total inhibition of plasma renin activity by the use of a specific renin inhibitor.[19] Thus, it appears far more likely that the difference in response resulted from an additional blood pressure-lowering mechanism when ACE was inhibited. One such mechanism is suspected to be the potentiation of bradykinin, but bradykinin has not been clearly demonstrated to accumulate in plasma during ACE inhibition.[20-22]

The most conclusive results were ultimately obtained by blocking the action of bradykinin by antibodies or specific antagonists. Using specific antibodies to bradykinin, bradykinin was shown to participate in the blood-pressure lowering produced by ACE inhibition.[23] In studies using competitive vascular antagonists of bradykinin[24] in renovascular hypertensive rats, we concluded that about a third of the hypotensive effect of enalapril was attributable to bradykinin.[25] Several studies using other ACE inhibitors or other bradykinin antagonists have confirmed these findings.[26,27]

Agents that antagonize vascular bradykinin receptors may also have partial agonistic properties for other bradykinin receptors, especially those in sympathoadrenal tissues.[28] Moreover, bradykinin exerts its vascular effects through β_1 and β_2 receptors and possibly additional unidentified receptors.[29] Some of these have direct effects on vascular smooth muscle, whereas others act by stimulating other vasoactive substances like endothelium-derived relaxation factor and prostaglandins. Therefore, it is complex to assess the relative contributions of bradykinin itself and those of the several other systemic and tissue hormones that it regulates to the blood pressure-lowering effects of ACE inhibition. Nevertheless, bradykinin is now generally thought to play a contributory role. The finding that excess body sodium suppresses the generation of kinins[30] further explains the loss of antihypertensive efficacy of ACE inhibitors after salt loading.

Another mechanism appears to participate in the long-term antihypertensive effect of ACE inhibition, that of the influence of the long-term blockade of angiotensin II formation on other vasopressor systems. All three major vasopressor systems—renin-angiotensin, sympathoadrenal, and vasopressin—are closely interrelated through neurohormonal pathways. Each pathway transmits positive or negative feedback to one or more of the others, affecting its release or responsiveness by acting as a neurotransmitter or neuromodulator or by exerting a permissive action on effector organs. For example, angiotensin II stimulates the release of catecholamines and vice versa. Long-term ACE inhibition blunts the pressor response of arterioles to sympathetic stimuli.[31] It also diminishes sympathetic activity, as evidenced by decreased levels of circulating norepinephrine and decreased turnover and tissue content of norepinephrine.[32] In this respect, ACE inhibitors exert pharmacologic effects opposite to those of other vasodilators, such as hydralazine or minoxidil, which cause reflex stimulation of the sympathetic system.

The clinical implications of these differences are important, as they may explain some of the different long-term effects of these drugs in various tissues. For example, ACE inhibitors can reverse hypertension-induced left ventricular hypertrophy,[33] whereas other vasodilators with equally good antihypertensive efficacy cannot. As another example, ACE inhibitors can reduce mortality in chronic congestive heart failure,[34] whereas most other vasodilators that successfully control symptoms of congestive heart failure do not seem to prolong life.[35] A hydralazine-nitrate combination did reduce mortality but was still less effective than enalapril.[36]

Vasopressin, on the other hand, appears to function as an important vasoconstrictor only when the renin-angiotensin and sympathetic nervous systems are effectively obliterated. Angiotensin II facilitated the release of vasopressin in response to stimuli, and captopril decreased plasma vasopressin levels.[37]

In general, changes in the release of or responsiveness to one factor lead to compensatory adjustments in plasma or tissue levels or receptor sensitivity of the others. Angiotensin-converting enzyme inhibition affects all these interdependent functions, which probably contributes to the final blood pressure response, the magnitude of which varies under various clinical conditions.

Possible Cardiac and Renal Problems

J. I. S. Robertson, MD*: The therapeutic efficacy of ACE inhibitors is well established.[38] They lower blood pressure predictably in patients with renovascular hypertension and, when combined with a loop diuretic, in those with severe and often resistant hypertension. Moreover, they can work effectively in treating essential hypertension, administered either alone or with a thiazide diuretic. In cardiac failure, they have diminished dyspnea, improved exercise capacity, reduced the prevalence of ventricular ectopic rhythms,[39] and prolonged survival.[34]

The side effects of ACE inhibitors are also well established.[38,40] Some problems apparently specific to captopril may relate to the thiol group in that compound; these problems were more prominent in the early days of therapy when unsuitable high doses of as much as 450 mg per day were used. The initial problems included neutropenia, agranulocytosis, proteinuria, the nephrotic syndrome, and Guillain-Barré neuropathy. These complications have receded with reduced doses of no more than 150 mg per day and further reduced doses in patients who have renal impairment. Nevertheless, taste loss or disturbance does remain a problem with captopril therapy, even at current lower doses, but it may occur less frequently. Guillain-Barré neuropathy has also been reported with the use of captopril at a dose of only 75 mg per day.[41] Side effects with ACE inhibitors as a class include morbilliform or urticarial rash, unproductive cough, occasional wheezing, angioneurotic edema, Raynaud's phenomenon, headache, dizziness, and syncope.[38,40]

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My principal concern here is not with the side effects of ACE inhibitors as such but rather with physiologic consequences inherent in the pharmacologic actions of these drugs. I shall consider such problems related to two organs, the heart and the kidneys.

Cardiac Effects

In both normotensive and hypertensive patients, circulating concentrations of angiotensin II are within a range having a direct, immediate effect on arterial blood pressure.[42] Thus, lowering angiotensin II levels with the initial dose of an ACE inhibitor was found to cause prompt and proportionate blood pressure reduction, significantly correlated with levels of renin or angiotensin II before therapy and with the fall of plasma angiotensin II levels at the early peak effect of the drug.[38,43] With more prolonged therapy, these correlations become looser,[38,43] as discussed by Dr Gavras earlier. Such consistent effects of the first dose raise clinical concern in patients with hypertension only when ACE inhibition therapy is introduced in those with high circulating angiotensin II levels, as with previous diuretic treatment[44] or in the hyponatremic hypertensive syndrome.[45] Angiotensin-converting enzyme inhibitors can then cause an initial steep, profound drop in arterial pressure, sometimes enough to imperil the cerebral circulation.

A rarer, less predictable, but potentially more serious problem relates to two other actions of angiotensin II, its facilitating action on the sympathetic nervous system[31] and its converse vagolytic effect.[46] The sudden and simultaneous removal of both of these actions with ACE inhibition can provoke severe hypotension, syncope, and bradycardia. An additional contributory factor, activation of the Bezold-Jarisch reflex,[47] has also been proposed. These events are especially likely when ACE inhibition is introduced in patients with cardiac failure, a condition resulting in sympathetic activation and, particularly if digitalis is administered, in potentially high vagal tone. The fall in blood pressure in these patients significantly correlates with the plasma angiotensin II concentration before ACE inhibition and with the subsequent fall in heart rate.[48] With syncope of this cause, plasma epinephrine levels increase, indicating stimulation of adrenal medullary secretion but no rise in the concentration of plasma norepinephrine.[49] First-dose hypotension has been regularly encountered in all the major trials of ACE inhibitors in cardiac failure, including the Cooperative North Scandinavian Enalapril Survival Study,[34] the second Vasodilator-Heart Failure Veterans Affairs Cooperative Study Group,[36] and the Studies of Left Ventricular Dysfunction.[50]

This sometimes disturbing syndrome has been treated by atropine sulfate administration and intravenous angiotensin II infusion.[48] It may, if uncontrolled, lead to cerebral, renal, or cardiac damage. Because the occurrence of the syndrome is not readily predictable, the use of a short-acting ACE inhibitor, such as captopril,[1] rather than a longer-acting one, such as lisinopril, enalapril, or ramipril, has been recommended. This approach will not prevent the occurrence but will facilitate treatment by limiting its duration. An alternate approach has been to reduce the initial dose of the ACE inhibitor.[34]

Renal Effects

Angiotensin II has potent, presumably important local actions on the kidneys. One route of its access to renal tissues is through renal arterial blood. In addition, all components of the renin-angiotensin system are present in the kidneys,[51,52] and locally generated angiotensin II can gain access to intrarenal structures in both renal blood and renal lymph. The latter routes could well be the more important.

Angiotensin II has been found in both afferent and efferent glomerular arterioles.[51] There is evidence that the efferent arterioles are disproportionately sensitive to the vasoconstrictor effects of angiotensin II.[53] Its receptors are especially profuse about the glomeruli and over the vasa recta bundles.[54] Two possible intrarenal functions of angiotensin II may be especially important when renal blood flow is imperiled. First, differentially enhanced tone at efferent arterioles helps to sustain the glomerular filtration rate despite a decreased renal blood flow.[53,55,56] Second, angiotensin II-mediated slowing of blood flow in vasa recta bundles could facilitate a countercurrent exchange between the descending arterial and the ascending venous limbs and between the ascending venous limbs and the descending thin limbs of the loops of Henle. This second function could be an important means of preserving urea excretion.[55,56] Although such functions are compensatory, a gross excess of local angiotensin II could clearly cause a shutdown of the circulation by both the glomeruli and the vasa recta and a rapid advance into renal failure.

Clinical Implications

Features common to three clinical syndromes—cardiac failure, sodium depletion, and renal artery stenosis—may activate the initially compensatory intrarenal actions of angiotensin II.[56,57] All three syndromes are often accompanied by elevated peripheral plasma concentrations of renin and angiotensin II. Moreover, renal blood flow is reduced; it is probable, but not demonstrated, that this diminished blood flow mainly traverses the deep nephrons. Initially, all three syndromes share a partial preservation of the glomerular filtration rate and a capacity to secrete urea. In renal artery stenosis, increased intrarenal renin sustains the renal arterial pressure distal to the stenosis.[58] All three conditions may terminate in renal failure, characterized by a pronounced rise in serum urea and creatinine levels and a fall in the serum sodium concentration. In renal artery stenosis, however, renal failure develops only if both kidneys are affected, if one kidney is absent, or if the rare hyponatremic hypertension syndrome is present.[45]

The normal gradient of renin across the kidney is lost in both renal artery stenosis[59] and sodium depletion.[60] The normally renin-poor deep glomeruli become rich in renin as the overall renin content of the kidneys increases. Although similar changes probably occur in cardiac failure, this phenomenon has yet to be studied. Renin appears in the deep nephrons at a time when renal performance comes to rely principally on these structures and when renal functional compensation evidently depends heavily on a local intrarenal action of angiotensin II.

If the foregoing speculations prove valid, then any clinical benefits accruing from ACE inhibition in cardiac failure or renal artery stenosis will, in most cases, be associated with some inevitable adverse renal consequences.[56,57] In patients with pure sodium depletion, ACE inhibitors could be predicted to be entirely harmful[61] and should not be given. In most cases of cardiac failure, ACE inhibitors do produce a range of benefits, as enumerated earlier; however, their use is

predictably accompanied by a consistent rise in serum urea and creatinine levels[36,39,50] for reasons explained earlier. Rarely, however, in a preterminal patient who presumably already has grossly excessive intrarenal renin, markedly elevated urea and creatinine levels, and hyponatremia, administering ACE inhibitors can understandably improve renal function and correct the hyponatremia.[62] In renovascular hypertension, ACE inhibitors can effectively control the elevation of systemic arterial pressure[43,57] and correct the pronounced biochemical abnormalities of the hyponatremic hypertensive syndrome.[45] The already impaired functioning of the afflicted kidney frequently worsens, however, with a fall in the glomerular filtration rate[63] and renal plasma flow.[57] In some patients, ACE inhibition may provoke renal artery occlusion.[57] In experimental renal artery stenosis in rats, ACE inhibition causes an already small poststenotic kidney to shrink further.[64]

Is the Role of Cardiovascular Risk Reduction Established in Hypertension?

WILLIAM MCFATE SMITH, MD, MPH*: Whether reducing cardiovascular risk factors lowers blood pressure is a question that is confounded by the implied assumption that the treatment of hypertension with ACE inhibitors has been shown to reduce risk. In the absence of such evidence, we must confront a compelling question: Must definitive trials be mounted to show that ACE inhibitors when used to treat hypertension reduce morbidity and mortality? Several subsidiary issues surround that question (not all of which will be addressed here):

- What is the standard—how effective are other agents in reducing morbidity and mortality?
- What evidence shows that blood pressure control per se reduces risk? and for which end points?
- Do ACE inhibitors have effects other than lowering blood pressure?
- Is there reason to think that a drug could lower blood pressure without reducing risk?
- How good is the evidence that blood pressure control lowers risk?
- Has this been shown for all other antihypertensive agents? Must it be?
- Are these issues only regulatory? or are they also scientific?

Diuretics and β-Blockers

We must first examine the evidence that pharmacologic lowering of blood pressure reduces the risk of cardiovascular complications in patients with mild to moderate hypertension. In 1986, MacMahon and co-workers reviewed designs and the results of 19 controlled studies with data on morbidity and mortality, including nine long-term, randomized, controlled trials published in the preceding seven years.[65] They assessed the consistency of these studies, measured changes in cardiovascular morbidity and mortality resulting from the drug treatment of hypertension, and analyzed pooled results from the nine most relevant studies.

The analysis of pooled results had a twofold rationale. First, most studies were designed to recognize treatment efficacy for combined cardiovascular disease end points, and event rates in individual studies were only sufficient to detect large treatment effects, such as those seen for cerebrovascular disease. Second, the size and event rates of most individual studies were inadequate to determine small (10% to 15%) reductions in either total mortality or fatal and nonfatal ischemic heart disease. Unlike the analysis of any single study, the analysis of pooled results provided more stable estimates of effects of treatment and greater power to detect relatively modest reductions in morbidity and mortality.

Pooled data were analyzed by calculating the difference between observed and anticipated events (treated versus control groups) and the variance of that difference for each trial and then summing results for all trials.[66] From these values, an odds ratio (z value) and 95% confidence intervals were calculated and were expressed in terms of percent change in risk.

The pooled analysis was based on about 43,000 patients with an average follow-up of 5.6 years. Sample sizes varied from 380 in the VA study[67] to more than 17,000 in the Medical Research Council trial.[68] Follow-up ranged from 1.5 years in the VA-National Heart, Lung and Blood Institute trial[69] to 7.5 years in the US Public Health Service Hospitals study.[70]

In these studies, the lowering of diastolic blood pressure was nearly 6 mm of mercury greater in the intervention than in control groups. Criteria for end points were assumed to be comparable in the pooled studies. Whereas comparability is certain for total mortality, it is less certain for cause-specific mortality or morbidity due to such causes as nonfatal myocardial infarction.[67-73] The two studies without untreated controls—the Hypertension Detection and Follow-up Program (HDFP)[74] and the Multiple Risk Factor Intervention Trial (MRFIT)[75]—differed from the others in that their con-

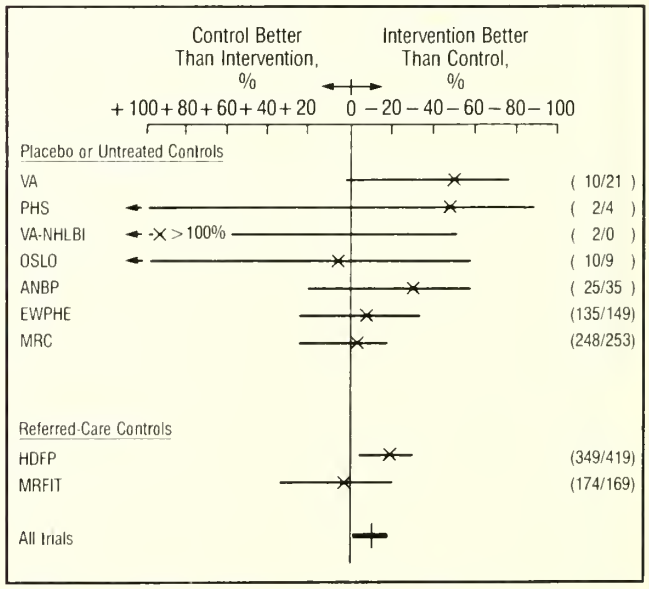

Figure 1.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in total mortality between intervention and control groups. The number of events (intervention/control) is given in parentheses (from MacMahon et al[65]). ANBP = Australian National Blood Pressure Study, EWPHE = European Working Party on High Blood Pressure in the Elderly, HDFP = Hypertension Detection and Follow-up Program, MRC = Medical Research Council Working Party, MRFIT = Multiple Risk Factor Intervention Trial, OSLO = Oslo Trial in Mild Hypertension, PHS = US Public Health Service Hospitals Cooperative Study Group, VA = Veterans Administration, VA-NHLBI = Veterans Administration-National Heart, Lung, and Blood Institute

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trol subjects received the standard treatment of their respective communities. Inclusion of HDFP and MRFIT was justified on the basis that it could only lead to underestimating treatment benefits.

In five of the seven studies with placebo or untreated controls, intervention lowered total mortality, but the reduction was statistically insignificant (Figure 1). The VA and Australian studies showed the strongest trends in reduced mortality. On the other hand, when data pooled from all seven trials were analyzed, total mortality in the treatment groups was 11% lower, and this reduction was statistically significant.

Intervention reduced the incidence of stroke deaths in the six of the seven studies for which an odds ratio could be estimated (Figure 2). This reduction was statistically significant in both the VA and HDFP studies. The same was true for the incidence of nonfatal stroke.

Treatment reduced the incidence of coronary heart disease mortality in four of the seven studies with untreated controls and in the HDFP (Figure 3). This reduction was statistically significant only in the European Working Party on Hypertension in the Elderly trial. In this trial, nominal significance was achieved for "cardiac deaths," a category including deaths from congestive heart failure as well as ischemic heart disease. The figures for nonfatal myocardial infarction were not reported separately. Pooled data analysis showed that treatment lowered coronary heart disease mortality by 8%, which was not statistically significant.

Results of these nine long-term randomized, controlled studies offer convincing evidence for benefits of therapy in terms of total mortality and stroke incidence, but benefits were, for the most part, attributable to an impressive reduction in stroke mortality. On the other hand, the evidence that

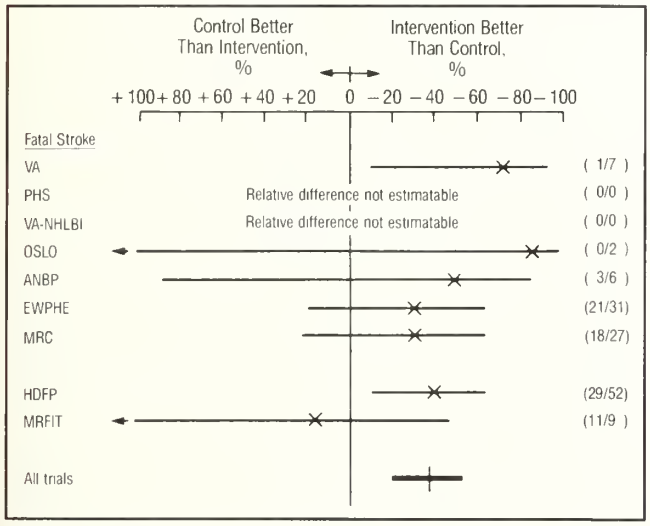

Figure 2.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in fatal stroke between intervention and control groups. The number of events (intervention/control) is given in parentheses (from MacMahon et al[65]). ANBP = Australian National Blood Pressure Study, EWPHE = European Working Party on High Blood Pressure in the Elderly, HDFP = Hypertension Detection and Follow-up Program, MRC = Medical Research Council Working Party, MRFIT = Multiple Risk Factor Intervention Trial, OSLO = Oslo Trial in Mild Hypertension, PHS = US Public Health Service Hospitals Cooperative Study Group, VA = Veterans Administration, VA-NHLBI = Veterans Administration–National Heart, Lung, and Blood Institute

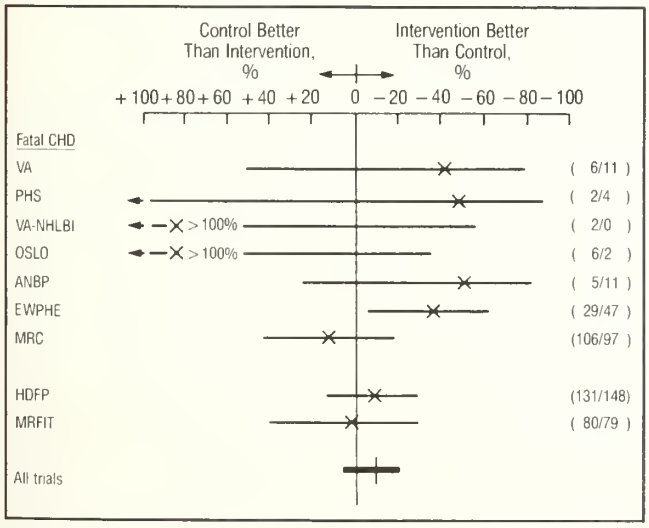

Figure 3.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in total coronary heart disease (CHD) mortality between intervention and control groups. The number of events (intervention/control) is given in parentheses. Data in the European Working Party on High Blood Pressure in the Elderly (EWPHE) were reported only as total cardiac mortality (from MacMahon et al[65]). ANBP = Australian National Blood Pressure Study, HDFP = Hypertension Detection and Follow-up Program, MRC = Medical Research Council Working Party, MRFIT = Multiple Risk Factor Intervention Trial, OSLO = Oslo Trial in Mild Hypertension, PHS = US Public Health Service Hospitals Cooperative Study Group, VA = Veterans Administration, VA-NHLBI = Veterans Administration–National Heart, Lung, and Blood Institute

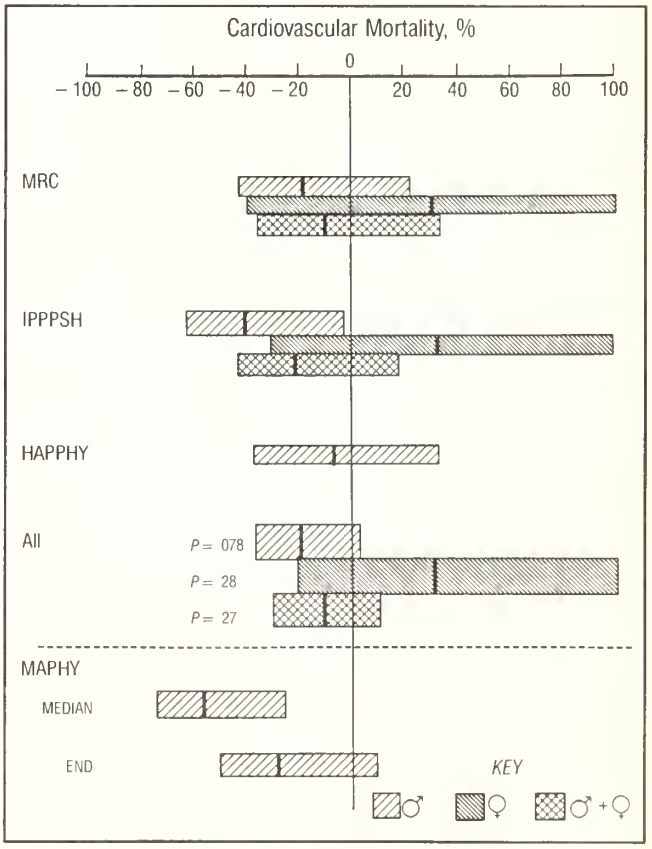

Figure 4.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in cardiovascular mortality among intervention and control groups by sex and by total study population in the Medical Research Council Working Party (MRC), International Prospective Primary Prevention Study in Hypertension (IPPPSH), and Heart Attack Primary Prevention in Hypertensives (HAPPHY) studies. Meta-analysis was used to determine pooled results of all three studies (All) by sex and by total study populations. The lower panel shows results for men in the Metaprolol Atherosclerosis Prevention in Hypertension (MAPHY) study (from MacMahon et al[65]).

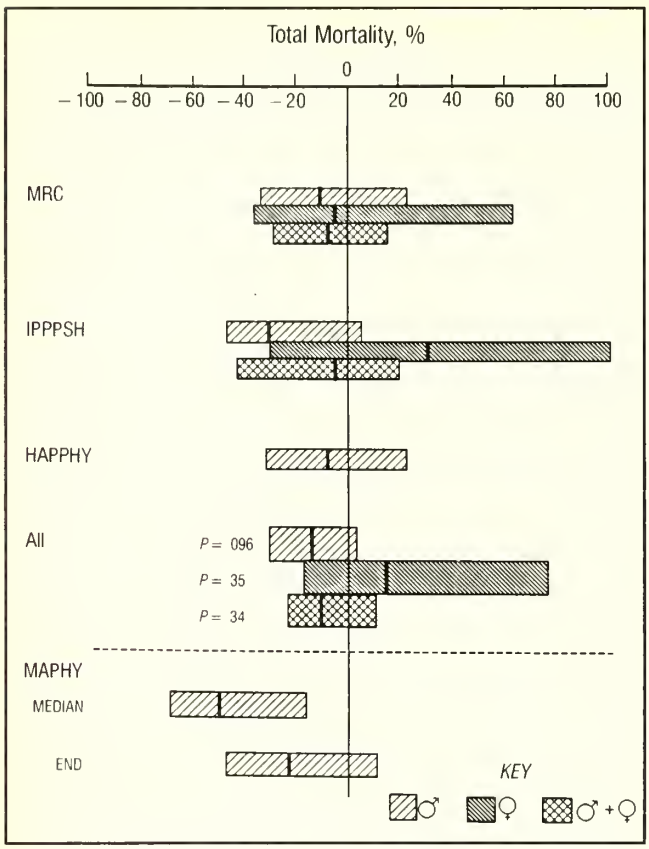

Figure 5.—Estimates, with approximate 95% confidence intervals, are shown for the relative difference in total mortality among intervention and control groups by sex and by total study population in the Medical Research Council Working Party (MRC), International Prospective Primary Prevention Study in Hypertension (IPPPSH), and Heart Attack Primary Prevention in Hypertensives (HAPPHY) studies. Meta-analysis was used to determine pooled results of all three studies (All) by sex and by total study populations. The lower panel shows results for men in the Metaprolol Atherosclerosis Prevention in Hypertension (MAPHY) study (from MacMahon et al[65]).

treatment prevents morbidity and mortality from coronary heart disease is unconvincing. A later report analyzed all available data from 13 unconfounded randomized trials of antihypertensive agents involving nearly 37,000 persons.[76] This report included eight of the nine trials in the MacMahon analysis (MRFIT was excluded because of a concomitant intervention on other risk factors) plus five others. The 13-trial analysis suggested a significant reduction ($P<.01$) in coronary heart disease events.

Three subsequent long-term clinical trials also evaluated the efficacy of blood pressure treatment to prevent complications of hypertension, bringing the total to 12 trials in the past decade. Despite the significant lowering of blood pressure reported in two of the three, the International Prospective Primary Prevention Study in Hypertension (IPPPSH)[77] and the Heart Attack Primary Prevention in Hypertensives (HAPPHY),[78] results failed to show any difference between diuretics and β-blockers in reducing total and cardiovascular mortality. Figures 4 and 5 compare cardiovascular and total mortality in the IPPPSH,[77] HAPPHY,[78] and Medical Research Council[68] trials with that in the controversial Metaprolol Atherosclerosis Prevention in Hypertension (MAPHY) study.[79] In all 12 recent trials, diuretics, β-blockers, or both were used to lower blood pressure. Moreover, the three latest studies (IPPPSH, HAPPHY, and MAPHY) compared the use of diuretics with that of β-blockers and did not include a placebo control group. Of these, only the MAPHY study showed a bottom-line difference between diuretics and β-blockers. In the Medical Research Council study, however, both diuretics and β-blockers produced better outcomes than placebo.

This review raises important questions: Why did individual studies fail to show benefits of blood-pressure lowering for coronary heart disease and total mortality? And why, even with meta-analysis, was minimal benefit shown for coronary heart disease? Some of the reasons may be as follows:

- The trials were too small. Even with pooling of data, clinically important effects on coronary heart disease (for example, a decrease of 15%) were not detected.
- The trials may have been too short; 5.6 years may not be long enough for blood pressure reduction to affect the incidence of atherosclerosis.
- The metabolic side effects of the drugs may have offset the benefits of blood pressure reduction. β-Blockers are known to reduce high-density–lipoprotein cholesterol levels and to increase low-density–lipoprotein cholesterol and triglyceride levels. Diuretics are known to increase total cholesterol and to decrease serum potassium and body magnesium levels.
- The widespread use of antihypertensive agents among control patients from these studies, particularly those using community control groups, may have reduced the estimates of true benefit.
- It has been proposed that differences in autoregulatory reserve and blood-oxygen extraction potential between the coronary and cerebral circulation may explain why antihypertensive treatment protects against stroke but not myocardial infarction.[80] This explanation is consistent with the report of a J-curve relation between death from myocardial infarction and treated diastolic blood pressure in hypertensive patients with concomitant coronary arteriosclerosis.[81]

Angiotensin-converting Enzyme

Is there any basis for thinking that ACE inhibitors might differ from diuretics and β-blockers? Is this question regulatory or only scientific? Worldwide, no regulatory agency requires that antihypertensive agents be shown to reduce morbidity and mortality to be licensed to treat high blood pressure. On the other hand, it is unlikely that any regulatory agency would permit an advertising claim that a particular drug provides cardioprotection in the absence of convincing data from one or more controlled trials designed to evaluate morbidity and mortality. Thus, in addition to answering the scientific question, there may be commercial interest in establishing that ACE inhibition reduces cardiovascular risk in hypertensive patients.

Before looking at the potential of ACE inhibitors in this regard, we should consider what diuretics and β-blockers do in addition to lowering blood pressure. We know that diuretics are effective in preventing or managing early congestive heart failure. We also know that they increase the incidence of ectopia and reduce renal blood flow. Whether or not they reverse left ventricular hypertrophy remains uncertain. β-Blockers have known cardioprotective effects in survivors of at least one myocardial infarction. Indeed, this finding formed the basis for the primary prevention studies (MRC, IPPPSH, HAPPHY) comparing diuretics and β-blockers. β-Blockers are known to reduce ectopia and to reverse left

ventricular hypertrophy; they may also reduce infarct size. On the other hand, they also reduce myocardial contractility and cardiac output, reduce renal blood flow, and affect related renal functions.

How does the use of ACE inhibitors compare with that of diuretics and β-blockers? They are as effective as thiazide diuretics and β-blockers in reducing blood pressure and maintain this effect without producing tolerance. This clinical efficacy is attributable to their unique humoral and hemodynamic effects, namely vasodilation without reflex activation of the sympathetic nervous system and without sodium retention; the most obvious consequences are no increase in heart rate and no edema. Additional evidence suggests that by unloading the left ventricle, ACE inhibitors can prevent damage or failure of the heart as a pump, can cause regression of left ventricular hypertrophy,[82] and can be effective in treating heart failure.[34,50,76]

By inhibiting endogenous angiotensin II formation and action, ACE inhibitors increase renal blood flow and reduce glomerular hydrostatic pressure while preserving the glomerular filtration rate.[83] Furthermore, in hypertensive patients with only modest renal dysfunction, long-term therapy with ACE inhibitors increases the glomerular filtration rate and renal blood flow and decreases renal vascular resistance.[84] Angiotensin-converting enzyme inhibitors may therefore exert a favorable influence on renal hemodynamics in the presence or absence of renal insufficiency.

But what of the morbidity and mortality from ischemic heart disease that diuretics and β-blockers have failed to prevent? Could ACE inhibitors prevent coronary atherosclerosis, ventricular arrhythmia, or sudden death? How do they influence the coronary circulation, and what is their effect in the presence of coronary disease? They can certainly remove hypertension as an atherogenic factor. Because they are lipid neutral and may suppress platelet aggregation in patients with essential hypertension,[85] they may have the potential to prevent coronary atherosclerosis. They neither activate the sympathetic nervous system nor deplete potassium; as a result, they may also have negligible potential for inducing malignant arrhythmias.[86] Indeed, both enalapril and captopril reduce the frequency of ventricular arrhythmias in congestive heart failure. Finally, ACE inhibitors may reduce myocardial oxygen demand and increase oxygen supply,[87] increase collateral blood supply to ischemic zones and decrease infarct size in dogs,[88] and prolong survival after myocardial infarction in rats.[89]

Do these data give us good reason to think that ACE inhibitors are superior to diuretics and β-blockers in reducing the risk of cardiovascular complications in patients treated for hypertension? Taken together, they suggest that ACE inhibitors may offer primary cardioprotection and may exert beneficial therapeutic effects in hypertensive patients with coronary heart disease. Are these data suggestive enough to compel us to consider a definitive long-term clinical trial that would have to be very large and thus very expensive? My answer is an unequivocal yes, both in terms of scientific importance and practical value for patients, to say nothing of the commercial consequences for manufacturers of this class of agents.

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Epitomes

Important Advances in Clinical Medicine

Pathology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in pathology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in pathology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Pathology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Human Prion Diseases

PRIONS ARE the pathogenic agents of a group of dementing diseases associated with the production of a unique amyloid protein called prion protein (PrP). Prion diseases are novel in that they are both transmissible, or infectious, and hereditary. These diseases are known by a variety of synonyms, including human spongiform encephalopathy, "slow" (unconventional) viral infections, and transmissible dementias.

Prion diseases are linked by several elements. The disease is limited to the brain; there is a lengthy asymptomatic period lasting years or decades; they have a progressive, uniformly fatal clinical course, without remission; they are transmissible to other mammals; and no specific clinical diagnostic tests or therapy exist.

Prion diseases are characterized mostly by spongiform changes in the brain, with varying degrees of PrP amyloid deposition, gliosis, and neuronal loss; there is no notable host inflammatory response.

Prions are highly resistant to inactivation by procedures that kill viruses and bacteria by denaturing nucleic acids, but they are inactivated by procedures that denature proteins, including 1N sodium hydroxide or hypochlorite solutions and autoclaving. Prion protein is a sialoglycoprotein encoded in DNA (but devoid of any nucleic acid) that undergoes a series of posttranslational modifications to produce an abnormal isoform; this polymerizes to form PrP amyloid. Although the precursor molecule of PrP is found in most human tissues, its normal function has yet to be elucidated.

Four human prion diseases are recognized: Creutzfeldt-Jakob disease, kuru, Gerstmann-Straussler-Scheinker syndrome, and fatal familial insomnia. Whereas the clinical symptoms vary, including dementia, ataxia, myoclonus, and insomnia, they are thought to represent variations of the same disease process.

The Gerstmann-Straussler-Scheinker syndrome and fatal familial insomnia are exceedingly rare diseases found in familial clusters, being transmitted in an autosomal dominant manner. Recent evidence indicates that both diseases are caused by several different single-codon substitutions in the PrP gene. These germline mutations result in a slightly abnormal PrP molecule, the presence of which is always lethal.

Kuru is a fascinating disease localized to the Fore region in New Guinea that has been shown to be transmitted by ritualistic cannibalism. The eradication of cannibalism should result in the extermination of the disease; no new cases have developed in persons born since cannibalism ceased. Hence, kuru appears to be an orally transmitted infection.

Creutzfeldt-Jakob disease is, by far, the most common prion disease, with an incidence of about 1 case per million people per year. The most dramatic cases of Creutzfeldt-Jakob disease are those wherein the infection has been iatrogenically transmitted, such as by corneal grafts, intracranial electrodes, cadaveric dura mater grafts, and the intravenous administration of growth hormone derived from pooled cadaveric pituitary glands. Also, well-defined familial clusters of Creutzfeldt-Jakob disease exist, such as in Libyan Jews, in whom the disease is transmitted in an autosomal dominant manner like the Gerstmann-Straussler-Scheinker syndrome or fatal familial insomnia. Most cases of Creutzfeldt-Jakob disease, however, are sporadic and thought to represent random mutations of the PrP gene.

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Hepatitis C Screening and Blood Safety

BLOOD TRANSFUSION IS now safer because of routine screening for the antibody to hepatitis C virus (anti-HCV). The risk of posttransfusion non-A, non-B hepatitis has dropped from as high as 1 in 100 to less than 1 in 3,300 per unit received since May 1990 when "first-generation" enzyme immunoassay (EIA-1) screening began. Although hepatitis C virus (HCV) is not the only virus capable of causing posttransfusion non-A, non-B hepatitis, it is thought to account for at least 90% of cases. Further improvement in safety is expected with the "second-generation" methodologic enzyme immu-

noassay (EIA-2), which replaced EIA-I in March 1992. Enzyme immunoassay 2 has improved specificity over EIA-1 with no loss of sensitivity, yielding fewer "false-positive" results, that is, reactivity without infection, based on follow-up studies of transfusion recipients and using "confirmatory" testing.

Investigational confirmatory techniques consist of an antibody detection using a modified Western blot (the recombinant immunoblot assay), a neutralization assay, and direct testing for HCV RNA by polymerase chain reaction. Blood specimens reactive by EIA-1 or EIA-2 have been shown to correlate with disease in the transfusion setting. Although the 40% to 70% falsely reactive rate with EIA-1 has been reduced significantly (to less than 30%) by the use of EIA-2, research efforts for improved "third-generation" techniques (still based on nonstructural proteins) are already under way. In addition, the control of specimen storage and handling is critical for valid testing.

More than 30 million units of donated blood have been screened with the EIA-1 anti-HCV test, resulting in the exclusion of between 120,000 and 330,000 (0.4% to 1.1%) blood donors who were unknowingly anti-HCV–reactive. Because nearly 50% of persons infected by HCV have asymptomatic but persistent liver damage, including chronic active hepatitis, cirrhosis, and even hepatocellular carcinoma, research to minimize or interrupt the natural course of this disease is indicated. Asymptomatic former blood donors provide an identified pool of potential subjects who would be directly benefited by such research efforts. Transfusion recipients of blood donated in 1992 can expect more than a 20-fold reduction in the risk of posttransfusion hepatitis because blood is screened for anti-HCV.

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Acquired Immunodeficiency Syndrome Vaccines

THE DEVELOPMENT OF AN effective vaccine against the human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) is urgent and difficult. A successful vaccine must protect against cell-associated and cell-free virus at genital mucosal surfaces and in the bloodstream and must exert broad protection against the tremendous genetic variation exhibited by the virus. Because we do not understand the nature of protective immunity against HIV or have an animal model of HIV-1–induced disease, we must rely heavily on animal lentiviral infections to guide us toward a deeper understanding of the pathogenesis of the virus and the development of an effective AIDS vaccine.

The picture from the animal lentivirus models, however, is still unclear. Using recombinant HIV-1 envelope vaccines, a few chimpanzees have been protected against infection with a low dose of the homologous strain (IIIB) of HIV-1, apparently by the induction of a threshold level of neutralizing antibodies. Similar recombinant envelope vaccine approaches, however, have not been generally effective in protecting against challenge infection in the other animal lentivirus models. In these other animals, the best protection has been achieved with vaccines made of inactivated whole virus or attenuated live virus, but the mechanism of protection remains uncertain and such whole-virus approaches are not considered safe or practical for humans.

The shortfalls of these experimental vaccines are important: they require at least three injections over several months; the immunity is rather short-lived (less than a year); and the protection does not extend to intravenous challenge with higher doses of cell-free virus, to intravenous infection with cell-associated virus, or to infection across an intact genital mucosa. None of the experimental HIV-1 vaccines have yet been tested in chimpanzees against widely divergent HIV-1 strains such as occur in nature. In general, the immune protection elicited by the experimental vaccines in animals appears to convey a complete block to infection after challenge. This type of "sterilizing immunity" may be required of a vaccine to prevent later viral activation and disease, but it may also explain why the protection is so limited and why antiviral cytotoxic T-lymphocyte activity is not usually induced by these vaccines. The induction of strong $CD8^+$ cytotoxic T-lymphocyte activity is almost certainly a requirement of any truly efficacious HIV vaccine, and this may depend on a live vector or an attenuated live virus approach.

In the United States, seven different phase 1 and 2 trials, using candidate HIV-I recombinant envelope vaccines and adjuvants, are under way in more than 500 volunteer uninfected people. Two trials use core peptides (p17 and p24), and one trial uses inactivated (gamma irradiation and β-propiolactone) envelope-deficient whole HIV-1. In general, these immunogens have proved safe and immunogenic, but they have induced mainly type-specific neutralizing antibody of short duration (less than 6 months) and low titer (less than that seen in natural infection) and no $CD8^+$ cytotoxic T-lymphocyte activity. Live vaccinia vaccine (HIV-recombinant envelope) priming followed a year later by boosting with an HIV-envelope subunit (expressed in baculovirus) has had some encouraging results, but the vaccinia vector would not be safe for large efficacy trials unless further attenuated. Also, live vaccinia vectors would not be effective in vaccinia-immune persons. None of these phase 1 or 2 HIV-1 vaccine candidates have elicited the strong, durable, broadly reactive humoral and cytotoxic T-lymphocyte immune responses needed to justify larger-scale efficacy trials.

On the optimistic side, several hundred HIV-seropositive but immunocompetent persons who have received the HIV gp160 vaccine after infection have generally responded favorably by generating antibodies and T cells that recognize new antigenic determinants in the envelope. Insufficient time has elapsed to determine whether this treatment will suppress viral replication and delay the onset of AIDS. Evaluating the safety and immunogenicity of various HIV-1 immunogens given to HIV-1–infected subjects will help determine the suitability of these materials for prophylactic vaccination.

The criteria for selecting vaccine candidates for efficacy trials are unsettled, and we must decide on the end points to be used: preventing infection or delaying or preventing disease. For the latter, we need to define surrogate markers to predict disease, such as quantitative virus load, that can be measured early after infection. It is hoped that further preclinical developments in the animal models using different viral immunogens, different adjuvants, different routes of antigen presentation (such as mucosal), novel live vectors

(such as bacille Calmette-Guérin and adenovirus), and novel recombinant DNA constructs may yet lead to promising efficacy results as a basis for large-scale testing. In the meantime, high-risk uninfected cohorts are now being recruited and the infrastructure put in place in the United States and abroad for efficacy tests of one or more of the most promising candidate HIV-1 vaccines that may become available in several years. The first vaccines used may be only partially effective, but their early introduction might still prevent many infections, reduce viral transmission, delay disease, and provide valuable information that could facilitate future vaccine development. Multiple vaccines that are tailor-made for the predominant HIV strain(s) circulating at different global sites may need to be tested simultaneously. A long-term commitment has been made to vaccine development; this must include realistic expectations and both preclinical and clinical trials.

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Laboratory Evaluation of Inherited Thrombotic Disorders

RECENT ADVANCES IN THE diagnosis of and therapy for thrombotic disease have focused attention on the consulting role of clinical pathologists in the laboratory evaluation of coagulation disorders. Patients referred for evaluation usually have venous thromboembolism, but some may have arterial thrombotic events. Inherited disorders that can be tested for in a coagulation laboratory may result from abnormalities in inhibitors of activated coagulation factors (antithrombin III, protein C, protein S), impaired clot lysis (dysfibrinogenemia, plasminogen deficiency, tissue-plasminogen activator deficiency, excess plasminogen activator inhibitor), or a metabolic disorder associated with vascular disease and thrombosis (homocystinuria).

Although only about 30% of patients with recurrent thrombosis have an inherited disorder identified, the yield of this evaluation can be improved by restricting it to young patients with recurrent thrombosis or patients with thrombosis and a positive family history. The laboratory evaluation should be deferred until two to three months after the acute event (to avoid acute-phase changes that may obscure a correct diagnosis) and after the patient has discontinued anticoagulant therapy. Many laboratories offer both functional and immunologic assays for evaluating these disorders. Because thrombotic disease may result from either quantitative deficiency or a qualitative abnormality of these proteins (for example, antithrombin III or protein C) and immunologic assays may yield normal results in patients with dysfunctional proteins, it is preferable to do functional assays that detect both types of disorders. Appropriate specimen collection, timing, and processing are critical, especially for fibrinolytic assays (tissue-plasminogen activator, plasminogen activator inhibitor). Deficiencies of proteins C and S and antithrombin III are thought to be the most common causes of inherited thrombosis. Previous studies indicating that fibrinolytic abnormalities were common causes of recurrent thrombosis have been recently challenged. A metabolic disorder, heterozygous homocystinuria, has been increasingly associated with arterial vascular disease and should be considered in middle-aged patients with premature arterial thrombosis.

One approach in the laboratory investigation of recurrent thrombosis is to first exclude acquired causes of hypercoagulability—hyperlipidemia, lupus anticoagulant, or malignancy. The presence of venous thrombosis should be initially evaluated with a functional protein C assay and a free protein S antigen assay. If the results of these tests are normal, a functional assay for antithrombin III can be done, followed by testing for dysfibrinogenemia. If the test results are normal, the fibrinolytic system could be evaluated.

Unexplained arterial thrombosis in young patients can be evaluated with an assay of plasminogen activator inhibitor activity, whereas middle-aged patients with premature arterial thrombotic events should be tested for heterozygous homocystinuria using a methionine loading test.

The importance of laboratory monitoring of anticoagulation has been emphasized by studies showing the clinical benefit of adequate heparin and warfarin therapy in treating thromboembolism. Because the responsiveness of commercial laboratory-activated partial thromboplastin time reagents may vary substantially, each laboratory should establish its therapeutic heparin range (activated partial thromboplastin time ratio, 1.5 to 2.5), so that it is equivalent to a heparin level of 200 to 400 U per liter (0.2 to 0.4 U per ml) by protamine titration. Despite the large body of published evidence indicating the clinical importance of using the international normalized ratio format in reporting laboratory prothrombin times, many coagulation laboratories do not use this format, leading to inappropriate anticoagulant therapy for many patients. Increased educational efforts will be necessary to inform practitioners and pathology personnel of the importance of rigorous laboratory control of anticoagulation.

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Enhancing Antibody and Its Role in Acquired Immunodeficiency Syndrome

ANTIBODIES AGAINST VIRAL proteins have traditionally been considered beneficial to the host by preventing infection. This principle has been the mainstay of modern vaccine development. It is now known, however, that certain antibody responses may not benefit the host but may, indeed, benefit the virus. One such phenomenon, antibody-dependent enhancement, increases the infectivity of a variety of viruses from several different families. Antibody-dependent enhancement can occur when nonneutralizing antibodies bind to viral surface proteins. The Fc portion of this antibody can then be bound by Fc receptors on macrophages. Viruses that are resistant to lysosomal degradation can then infect macrophages by this route. A second mechanism has been described whereby nonneutralizing antibodies bind to viral

surface proteins and activate the complement cascade. Complement proteins, specifically C3, are fixed to the virus. This opsonized virus can then bind to complement receptors on macrophages, lymphocytes, or follicular dendritic cells. The virus can thereby infect these cells through this pathway.

Although in vitro antibody-dependent enhancement has been reported for a number of viruses, it has been difficult to show enhanced infections in vivo. The best documented example is dengue virus where clinically substantial dengue hemorrhagic fever and dengue shock syndrome occur in the presence of enhancing antibodies. Indeed, the severity of disease was correlated to the levels of enhancing antibodies. In vitro and in vivo antibody-dependent enhancement has been described for a number of animal viruses as well and is an important concern in veterinary vaccine development. This phenomenon of antibody-dependent enhancement and the viruses for which it has been observed were recently reviewed.

Infection by the human immunodeficiency virus (HIV) is accompanied by potent host immune responses against the virus. Early in HIV infection, patients have measurable neutralizing antibody titers, antibodies that can lyse HIV-infected cells, and cytotoxic lymphocytes that can kill virus-containing $CD4^+$ lymphocytes. In theory, all of these responses should combine to eradicate HIV infection in the host. Nevertheless, despite these immune responses, persons infected by HIV continue to progress through the full gamut of HIV-induced disease and finally die of complications of the acquired immunodeficiency syndrome (AIDS). This fact led investigators to search for possible adverse immune responses that may complicate the host response to HIV infection. In 1987, investigators first reported antibody-dependent enhancement of HIV infection in vitro. Later reports indicated that this enhancement could occur through both the complement and Fc receptor-mediated mechanisms. It has been difficult, however, to show a clear clinical role for enhancing antibodies in HIV infection. The best data on the role of enhancing antibodies in HIV-induced disease may come from studies using animals. Two separate studies using rhesus macaques and the simian immunodeficiency virus (SIV) have shown that enhancing antibody levels increase throughout the disease course and peak before death of the animals from AIDS. This animal model is arguably the best one for HIV infection. It has also been shown that chimpanzees infected with HIV have antibodies that can enhance HIV infection in vitro. Nevertheless, these antibody levels appear to decline the longer the chimpanzee is infected. Chimpanzees do not go on to have AIDS, nor do they become clinically ill following HIV inoculation.

Formidable difficulties are involved in studying enhancing antibodies in a disease that takes years to become clinically apparent. The average length of time for patients to progress to AIDS is 12 years. Even if high levels of enhancing antibodies resulted in a change in disease progression from 12 years to 8 years, it would require a huge clinical sample.

The greatest concerns to practitioners involve the theoretic risk of antibody-dependent enhancement in HIV infection. To date, no one has yet proved that in vivo enhancing antibodies of HIV infection do or do not play a role in disease progression. Circumstantial evidence such as disease progression despite potent immune responses to HIV and vaccine failure in animals suggests that in vivo antibody-dependent enhancement may be a reality. Can the theoretic risks be ignored, thus placing thousands of lives at risk if mass inoculation is given to persons in HIV-endemic areas with vaccines that produce antibody-dependent enhancement?

Despite the protestations of some investigators, mass immunization of many persons in high-risk areas of the world with vaccines that have proved ineffective in animals may occur. If these immunized patients show an increased susceptibility to HIV infection, then enhancing antibodies are important. If such studies progress as planned, we can only hope that antibody-dependent enhancement of HIV infection, unlike dengue virus, will be only an in vitro artifact. At this time, possible risks outweigh any demonstrated benefits to the putative AIDS vaccine being tested. A quick cure is not in sight for this pandemic.

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Iron Deficiency

STUDIES HAVE ASSOCIATED iron deficiency with epithelial changes, impaired immune response, abnormal temperature regulation, deranged catecholamine metabolism, and abnormal physical activity independent of any anemic effects. More recent studies have shown behavioral changes, reduced exercise tolerance, decreased levels of the neurotransmitter γ-aminobutyric acid in brain, altered lipid metabolism, and abnormal myelination of the central nervous system. Many of these diverse effects are reversible with iron therapy, whereas others may be partially reversible or permanent.

Of particular interest has been the effect of iron deficiency on the central nervous system independent of any concomitant anemia. Some parts of the brain contain considerable quantities of iron; iron is required for the activity of enzymes such as hydroxylases and monoamine oxidases that are important in brain function. Iron also influences myelination by its effects on lipid metabolism, causing changes in the fatty acid composition and content of lipids in both peripheral circulation and brain. Brain sphingolipid of iron-deficient animals has shown a pronounced reduction of fatty monoenoic acids such as ω9,C18:1 and ω9,C24:1. Iron supplementation of deficient animals results in at least a partial correction of these deficits. Iron is an essential requirement for desaturase enzyme function in liver, and iron deprivation might be expected to depress comparable desaturase activity in the fetal and neonatal brain. Observations to date show that iron deficiency is associated with dramatic changes in the fatty acid composition of myelin-specific lipids such as cerebroside.

Extensive studies done in children and adults indicate disturbances of behavior and cognitive factors with iron deficiency alone. In one study series, infants having iron deficiency with and without anemia tended to score lower in the Bayley scale of mental development than those without sideropenia. A clear sensory disturbance of taste has been well documented in adults with iron deficiency with and without

anemia eventuating in pica. A striking form of this disorder is a compulsive craving for ice, or pagophagia. The craving can be corrected with iron therapy before the correction of any accompanying anemia. The links between any neurologic clinical manifestations of iron deficiency and demonstrated biochemical abnormalities are tenuous, but the information to date would justify renewed clinical concern about the status of iron nutrition in people and especially in young children or neonates.

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Molecular Techniques

ONCE A FRINGE, highly specialized, and esoteric area largely relegated to basic research, DNA-based diagnostic techniques are now applied routinely to anatomic and clinical pathology tests. These techniques involve the manipulation of DNA for the purpose of detecting nucleotide sequences of clinical or forensic importance. These sequences are typically detected by hybridization (specific nucleotide base-pairing) with fragments of DNA or RNA (called probes) containing the complementary sequence. With the isolation (or cloning) of an ever-expanding array of disease-specific genes and sequences, a process now accelerating rapidly under the impetus of the human genome project, the list of available molecular pathology tests is growing weekly.

Specific molecular reagents now exist for the laboratory diagnosis of more than 100 genetic diseases, a myriad of infectious pathogens, tumor markers of diagnostic or prognostic importance, and the generation of individual-specific DNA fragment patterns (fingerprints) for paternity testing, forensic identification, twin zygosity determination, and transplant engraftment confirmation. The target for these hybridization reagents may be crude extracts of blood, tissue or body fluid DNA (the dot blot), electrophoresed fragments of restriction endonuclease-digested genomic DNA (the Southern blot), routinely processed tissue sections mounted on glass slides (in situ hybridization), or even metaphase or interphase chromosome spreads (molecular cytogenetics). Applications include the rapid identification of infectious agents (such as mycobacteria) without the need for lengthy microbial culture and biochemical species characterization procedures, prenatal diagnosis and carrier testing for genetic disorders (such as cystic fibrosis), and the diagnosis and staging of neoplastic processes by the detection of characteristic gene rearrangements and alterations in oncogenes and tumor suppressor genes (such as lymphoma and adenocarcinoma of the colon).

Spanning all of these applications, the use of the polymerase chain reaction continues to revolutionize the field, enhancing both the sensitivity and specificity of molecular techniques by many orders of magnitude. By replicating discrete regions of genomic DNA with DNA polymerase, the technique amplifies exponentially the amount of analyte available for study, allowing testing of the most minute clinical specimens (even single cells) while enabling one to home in on the specific region or target sequence of interest. It greatly simplifies the search for mutations associated with genetic diseases and malignant neoplasms and for microbial pathogens present in sparse infections (for example, human immunodeficiency virus in blood) and in dead or fixed specimens that are no longer culturable. The polymerase chain reaction can also be applied to DNA fingerprinting (by amplifying hypervariable regions of the human genome), allowing the identification of trace or degraded forensic specimens. By enabling genetic analysis of single cells, it has opened the way for preimplantation and even preconception diagnosis.

Like any new technology, molecular pathology has some drawbacks. Many of these tests are technically difficult, time-consuming, and expensive, requiring specialized resources and personnel often unavailable outside large academic centers and reference laboratories. Numerous ethical issues arise, impinging on matters such as genetic privacy, abortion, insurability and stigmatization, patent rights, and eugenics. Despite these challenges, diagnostic DNA techniques have already transformed and revitalized the practice of pathology in many exciting ways.

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Alerts, Notices, and Case Reports

Eosinophilic Meningitis Associated With Coccidioidomycosis

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COCCIDIOIDAL MENINGITIS represents an important cause of morbidity and mortality in the regions where *Coccidioides immitis* is endemic. Unfortunately, the diagnosis of coccidioidal meningitis may not be easily determined, especially during the early workup of a patient if the disease is unsuspected. Untreated, it leads to progressive debilitation and eventually death.[1] In this report we describe the cases of three patients who presented with coccidioidal meningitis and were found to have eosinophilic pleocytosis. This finding could be an aid in drawing clinicians' attention to this treatable condition.

Report of Cases

Case 1

The patient, a 42-year-old man, was seen because of worsening headache and drowsiness that progressed to coma over the course of three days. Two weeks before admission, he was treated with a course of oral antibiotic for pneumonia. At presentation, his temperature was 38.9°C (102°F). He was found to have nuchal rigidity, a positive Kernig's sign, and his level of consciousness was categorized as Glasgow coma scale 7. The rest of the physical findings, including those of the chest examination, were normal. A lumbar puncture revealed an increased opening pressure of 45 cm of water. The cerebrospinal fluid (CSF) glucose concentration was 1.4 mmol per liter (25 mg per dl; normal 2.8 to 4.4) with a blood glucose level of 5.4 mmol per liter (97 mg per dl); a protein of 1.26 grams per liter (126 mg per dl; normal <0.40); and a leukocyte count of $1,835 \times 10^6$ per liter (1,835 per μl) with a total eosinophil count of 569×10^6 per liter, or 0.31 (569 cells per μl, or 31%). The rest of the leukocyte differential consisted of lymphocytes, 0.46; neutrophils, 0.15; and monocytes, 0.08. The complement fixation (CF) test in the CSF yielded a coccidioidal antibody titer of 1:4. The CSF culture was negative for *C immitis*. The peripheral blood showed a total eosinophil count of 300×10^6 per liter (300 cells per μl) and a serum CF titer of 1:16.

The patient was started on a course of penicillin without any improvement. Two days later, following the reporting of complement in the CSF, a regimen of fluconazole was started at a dose of 400 mg daily. This resulted in gradual improvement, and he was discharged home after two weeks. Four weeks after discharge, a CSF examination showed a total leukocyte count of 505×10^6 per liter with a total eosinophil count of 66×10^6 per liter (0.13), the rest of the leukocytes being mononuclear cells. He continues on a regimen of oral fluconazole, and his general condition and neurologic status are at baseline.

Case 2

The patient, an 18-year-old woman, was referred for the evaluation of fever for a week following a cesarean section. The fever persisted despite triple-antibiotic therapy and heparinization for the possibility of pelvic thrombophlebitis. On physical examination, she was found to have nodular lesions on her trunk and arm, which had first appeared a month before delivery. On histopathologic examination, a nodule showed noncaseating granulomata with *C immitis* spherules. The patient had a lumbar puncture, which showed an increased opening pressure, a glucose content of 1.5 mmol per liter (27 mg per dl), with a blood glucose level of 5.4 mmol per liter (98 mg per dl); a protein of 0.55 grams per liter (55 mg per dl); an increased total leukocyte count of 588×10^6 per liter with a total eosinophil count of 364×10^6 per liter, or 0.62; and a CF titer of 1:8. The rest of the leukocyte differential count was lymphocytes, 0.26; neutrophils, 0.11; and monocytes, 0.01. She had peripheral eosinophilia with a total eosinophil count of $1,476 \times 10^6$ per liter, and the serum CF titer was 1:256. She was treated with a regimen of 400 mg of oral fluconazole daily. She defervesced over a period of seven days and was discharged without any neurologic abnormalities. Four weeks after discharge, CSF analysis revealed a leukocyte count of 62×10^6 per liter with a total eosinophil count of 7×10^6 per liter, or 0.09, and a CF titer of 1:8. The remainder of the leukocyte differential showed 0.87 lymphocytes and 0.04 monocytes. The patient did not report any complications, and she is functioning normally.

Case 3

The patient, a 33-year-old man, was seen because of progressively increasing headache and photophobia after recovering from a flulike illness. On physical examination he was afebrile and alert without nuchal rigidity or other signs of meningeal irritation. A funduscopic examination revealed no abnormalities. Otherwise the physical findings including the neurologic system were normal. A computed tomographic scan of the head was normal, and a lumbar puncture yielded clear CSF with glucose concentration of 1.2 mmol per liter (22 mg per dl) with a blood glucose level of 4.3 mmol per liter (78 mg per dl), a protein content of 0.78 grams per liter (78 mg per dl), increased leukocytes to 710×10^6 per liter with a total cosinophil count of 106×10^6 per liter, or 0.15, and a CF titer of 1:4. The peripheral blood showed a normal eosinophil count and a serum CF titer of 1:32. The patient was treated with a regimen of intravenous and intracisternal amphotericin B. After a predetermined total dose of 4 grams of amphotericin B, he was continued on a regimen of 400 mg of oral fluconazole. Two weeks after discharge, a CSF analysis revealed a leukocyte count of 430×10^6 per liter with a total eosinophil count of 30×10^6 per liter, or 0.07. The remainder of the leukocyte differential was lymphocytes, 0.85, and monocytes, 0.08. On the most recent follow-up visit, no complications were noted, and the patient is functioning normally.

(Ismail Y, Arsura EL: Eosinophilic meningitis associated with coccidioidomycosis. West J Med 1993 Mar; 158:300-301)

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ABBREVIATIONS USED IN TEXT

CF = complement fixation
CSF = cerebrospinal fluid

Discussion

Finding eosinophils in the cerebrospinal fluid is an uncommon event, seen in less than 3% of all CSF specimens.[2] Furthermore, as this finding is seen in a limited number of conditions, it can be helpful in alerting physicians to the possibility of a specific diagnostic consideration,[3] particularly when Kuberski's criterion of more than 10×10^6 per liter of eosinophils in CSF is used. Worldwide, the most frequent conditions associated with eosinophilic pleocytosis include helminthic infections, in particular infection with *Angiostrongylus cantonensis, Toxocara canis* and *Toxocara cati, Schistosoma* species, and *Paragonimus westermani.* Other central nervous system infections including *Mycobacterium tuberculosis, Histoplasmosis capsulatum, Toxoplasma gondii,* and rickettsial infections have been reported as causing eosinophilic pleocytosis. Rare but recognized causes include also neoplasms such as lymphoma and leukemias, allergic reactions to contrast agents, and drugs such as ibuprofen and ciprofloxacin.[5-7] The patients we have described presented in a recent nine-month period during an outbreak of coccidioidomycosis in Kern County. They were diagnosed and treated at Kern Medical Center, which serves the southern San Joaquin Valley, historically an area endemic for *C immitis* infection. On literature review, we found that the association of eosinophilic pleocytosis in the CSF of patients with coccidioidal meningitis has been infrequently reported.[8-10] We think, however, that this occurrence is much more common than has been previously reported, especially in light of the fact that three cases with this finding have been observed in a relatively short time. In addition, in a recent retrospective review of the records of 27 patients diagnosed at Kern Medical Center by a positive complement fixation test in the CSF during the past five years, we found that 8 (30%) of the patients had more than 10 eosinophils $\times 10^6$ per liter in the CSF (unpublished data). The major importance of this finding is that it provides a clue to the possibility of coccidioidal meningitis, which otherwise can be a diagnostic challenge. The diagnostic significance is more apparent when one considers the uniform mortality of the disease if the diagnosis is overlooked.

In summary, the finding of eosinophilic pleocytosis in the CSF is of diagnostic value for coccidioidal meningitis, particularly outside the endemic area. This finding should alert clinicians to review the historical travel data and consider the appropriate serologic and CSF testing. Further studies are needed to find the frequency of this observation as well as its prognostic value and additional clinical importance.

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Successful Medical Treatment of an Infected Prosthetic Aortic Graft

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INFECTIONS OF prosthetic arterial grafts are uncommon but carry a substantial risk of morbidity and mortality.[1-5] Death rates are 16% to 75%, depending on the site of involvement, and limb amputation rates are 11% to 75%.[3,6-8] The ideal management of infected arterial grafts is surgical excision of the involved segment, the placement of an alternative vascular supply, and systemic antibiotic therapy.[3,9-13] In several recent articles, less radical surgical techniques have been proposed, such as local debridement with wide incision, continuous irrigation with povidone-iodine and antibiotic solutions, and the use of gentamicin beads.[2,4,12,14] Rarely has medical therapy after percutaneous diagnostic aspiration or catheter drainage resulted in long-term control or apparent cure of infection. We report a case of periaortic graft infection associated with bacteremia caused by *Bacteroides* species that was successfully treated by percutaneous aspiration and prolonged antibiotic therapy.

Report of a Case

The patient, a 67-year-old woman with coronary and peripheral vascular disease, had an aortoiliac woven Dacron graft placed for a ruptured abdominal aortic aneurysm in August 1987. Her postoperative course was complicated by nosocomial pneumonia and multiple intra-abdominal abscesses requiring three additional operations. A computed tomographic (CT) scan three months after the initial operation showed total resolution of the abscesses and an intact graft.

The patient did well until 31 months later when she was readmitted for fever as high as 39.4°C, fatigability, and low back and left flank pain. She had a blood pressure of 158/84 mm of mercury, a pulse rate of 88 beats per minute, respirations 24, and temperature 39.3°C (103°F). On physical examination she had mild tenderness in the left lower quadrant, normoactive bowel sounds, no pulsatile mass, no hepatosplenomegaly, and several well-healed surgical scars. Peripheral pulses were diminished in the right lower extremity. Initial laboratory data included a leukocyte count of 11.5×10^9 per liter (11,500 per μl), a hemoglobin of 135 grams per liter (13.5 grams per dl), and hematocrit 0.40 (40%). The erythrocyte sedimentation rate was 115 mm per

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hour. Abdominal plain films showed feces in the colon without free air or bowel obstruction. A urinalysis was negative, as were cultures of urine for pathogens. After blood specimens were obtained for culture, a regimen of intravenous cefotetan disodium was started.

A CT scan of the abdomen and pelvis showed a streaky periaortic area of low attenuation along a 3-cm segment of the infrarenal aorta consistent with postinflammatory changes or graft infection. No gas was seen. After 48 hours of cefotetan therapy, the patient remained febrile, and therapy was changed to a combination of imipenem and cilastatin sodium given intravenously, without improvement. An indium scan was normal. On hospital day 7, blood cultures were positive for *Bacteroides* species. Her antibiotic regimen was switched to intravenous clindamycin phosphate and ceftazidime. A follow-up CT scan of the abdomen with an oral contrast medium showed an increase in the size of the collection around the graft (Figure 1). A gallium scan defined a

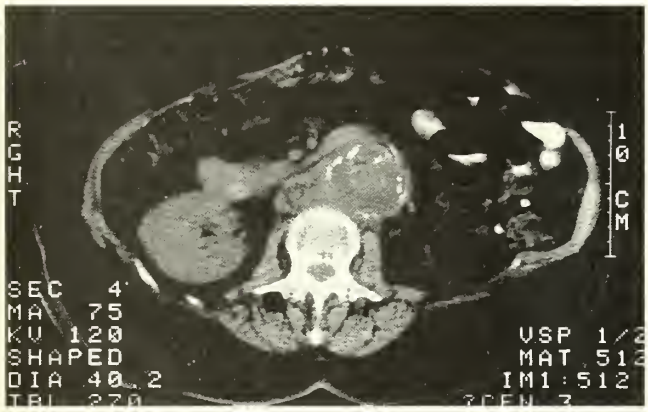

Figure 1.—A computed tomographic scan of the abdomen and pelvis shows streaking of the periaortic area overlying a vascular graft prosthesis with definite collection around the graft.

large area of uptake involving the posterior midabdomen consistent with the appearance on the CT scan. By day 16, she remained febrile, and a CT-guided fine needle aspiration of the periaortic graft fluid drained 30 ml of gray-green purulent material (Figure 2). A Gram's stain showed many neutrophils and rare gram-positive cocci but subsequently grew only *Bacteroides fragilis*. The patient refused surgical treatment and was continued on intravenous antibiotic therapy from which she had clinical improvement. The total course of intravenous drug therapy was about four weeks, of which

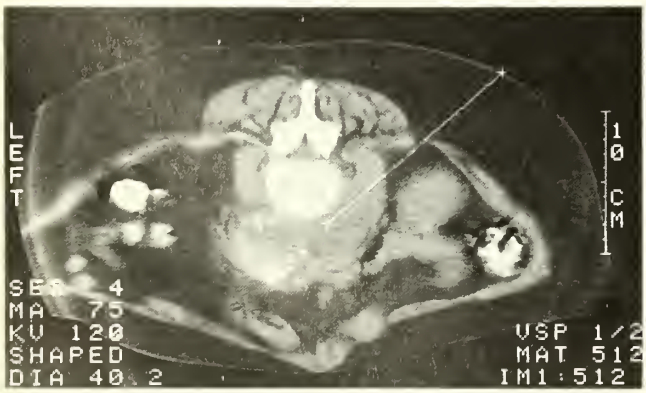

Figure 2.—On hospital day 16, a computed tomographic scan-guided fine needle aspiration of the collection around the graft drained purulent material infected with *Bacteroides* species.

approximately two weeks was following drainage. She was then discharged on a regimen of oral penicillin and metronidazole. Subsequently the patient showed complete radiologic resolution of the infected periaortic fluid collection (Figure 3).

Peripheral neuropathy developed that was related to prolonged metronidazole use, which has slowly resolved since discontinuation of the drug. Oral antibiotic modifications have been made, and the total course duration to date is about 26 months. She continues to do well, and both her sedimentation rate and leukocyte count have returned to normal.

Discussion

The incidence of prosthetic vascular graft infections depends on implant location. Rates are highest with aortofemoral grafts and may reach 5.9%.[9] Aortoiliac graft infections are the most difficult to diagnose, particularly when symptoms are primarily systemic. Infections can produce only nonspecific symptoms, have an indolent course, and only nonlocalizing findings may be elicited on physical examination.

The goal of treatment of an infected graft is to preserve life and to prevent limb-threatening ischemia.[1,2] The three aspects of this approach have traditionally been the removal of all or part of the graft, revascularization, and antibiotic therapy. Indications for graft removal are controversial. Generally, graft excision is warranted when there is thrombosis or evidence of peripheral embolization. Similarly, when

Figure 3.—A 16-month follow-up computed tomographic scan of the abdomen shows resolution of the graft infection.

there is involvement of the aortoiliac bifurcation, when anastomoses are infected, or when a vasculoenteric fistula is present, the ideal approach is to remove the entire graft. Such surgical intervention carries an immediate postoperative mortality of 16% to 35% so that less aggressive surgical treatment has been attempted with varying results.[5,15] Using continuous irrigation with povidone-iodine or an antibiotic has rarely resulted in cure.[14,16]

Antibiotics are generally considered adjunctive to surgical approaches in the management of graft infections.[17] Some data, however, appear to justify their use in the absence of major surgical intervention. In dogs, antibiotics that preferentially concentrate in leukocytes, such as clindamycin and rifampin, have effectively cleared graft infection.[18] Another

study in which gentamicin beads were implanted on both sides of the graft in the groin after debridement resulted in the control of infection.[4]

In the absence of prosthetic material, successful results of the nonsurgical drainage of abdominal abscesses have been well documented.[8,19-21] Only two cases of nonsurgical antibiotic therapy for periaortic graft infection have been previously reported, however, and both involved high-risk patients. Neither case involved anaerobes. Tobin successfully treated a patient with methicillin-resistant *Staphylococcus aureus* retroperitoneal abscess surrounding the femoral limb of an aortofemoral graft by placing a percutaneous drain and instituting systemic antibiotic therapy.[17] Matley and co-workers reported the resolution of early *Klebsiella* species aortic graft infection after percutaneous catheter drainage and the daily instillation of antibiotics plus systemic therapy.[14]

Our patient represents the third treated only with percutaneous drainage and prolonged antibiotic therapy. The CT scan taken during the course of her illness showed a ring-enhancing wrap of the abscess with low attenuation signals within and surrounding the opacified graft. No aortoenteric fistula or leaks were identified. These findings are in keeping with a true graft infection. Surgical intervention was deemed necessary, but the patient refused. She has done well on prolonged antibiotic therapy, and at 26 months' follow-up has no evidence of residual infection. In this patient, the choice of antibiotics was not under our control. Cefotetan therapy was presumably initiated as broad-spectrum coverage for many likely pathogens from a variety of sites. Imipenem-cilastatin was probably used next to broaden therapy in a patient who remained febrile despite a regimen of cefotetan. After identification of a *Bacteroides* species from blood cultures, the choice of clindamycin plus ceftazidime added little to previous choices. When the decision was made to switch to oral therapy, the choice of metronidazole plus penicillin was based on the identification of a *Bacteroides* species (metronidazole) plus the presence of unidentified gram-positive cocci (penicillin) on a Gram's stain that could have represented peptococci or peptostreptococci.

In summary, percutaneous drainage plus prolonged antibiotic therapy is an alternative to graft removal in selected patients. It should not be considered the therapeutic approach of choice, however. It appears most warranted in selected high-risk patients without septic thromboembolism or vasculoenteric fistulae and when anastomoses are spared. Computed tomographic scans should be used to follow the course of treatment. The failure to resolve, ongoing bacteremia, and persistent sepsis would be some of the indications to reassess this approach. The optimal duration of antibiotic therapy is unknown, and we cannot say with certainty that even at 26 months this patient is "cured." Thus, we have elected to treat indefinitely, but conceivably antibiotic therapy could be discontinued when there is neither radiographic, laboratory, nor clinical evidence of residual infection. Prospective studies are needed both to better define patients who do not need surgical intervention and to identify the optimal duration of antibiotic therapy.

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Editorials

AIDS—Science, Medicine, and Metaphor

Adapted from The John Alexander Lecture presented at the University of Pennsylvania School of Medicine, Philadelphia, September 29, 1992.

I WILL COMMENT on the AIDS [acquired immunodeficiency syndrome] epidemic from the vantage point of science, medicine, and metaphor. Along the way I will touch on the health care system, the "new virus," and a few other matters, but my overall goal is to persuade that AIDS is not "just another disease." Our response thus far has fallen terribly short. The discordance between biomedical scientific prowess and its application to the well-being of our people has reached an extreme point that requires rethinking. I will focus on AIDS because of who I am and what I do,* but for most of the problems and trouble spots of which I speak, the only thing new is the virus.

In just 11 years, a quarter of a million Americans have been diagnosed with AIDS; more Americans have died of this disease already than in the Korean and Vietnam wars combined; and the number of people now infected with the human immunodeficiency virus (HIV) is so great that we will soon exceed the death toll of World War II. Were there not another new instance of HIV infection beginning tomorrow, we would have our work cut out for us for the next decade just caring for those who are already on their way to illness.

If we do not realize that fully, it is because we have yet to embrace the fact that we must care. I am regularly astonished when politicians soberly discuss whether we can afford to care for people with AIDS—for the inference is that we have some choice. What alternatives do they have in mind? The issue is not whether but how, for the people with HIV infection are there, and they will need care.

Belinda Mason was a beloved colleague of ours on the National Commission on AIDS who died just a year ago at the age of 33. Before her illness became terminal, she had been a journalist and served as president of the National Association of People With AIDS. Throughout the two years I knew her, she expressed a profound wisdom I grew to value deeply. Once, when she was talking about the epidemic of fear and the resulting rejection and denial that so harass people trying to live with HIV infection, she commented that what we should really fear about AIDS is our society's failure to respond appropriately with care and compassion, for while we might in time learn to help people survive with HIV, in all of human history (she said), no society has ever survived that.

She went on to say,

> . . . people living with AIDS and HIV want nothing more or nothing less than what all of you take for granted . . . a place to live, the right to have a job, decent medical care, and to live our lives out without unreasonable barriers. We are not asking for extras, only to be included in what America already delivers to her privileged people.

We have learned much that we can or could do, including the most crucial of all—how to prevent HIV infection by avoiding risk. And yet, our Department of Health and Human Services predicts that there will be at least 45,000 but perhaps 80,000 new infections *per year* during this decade. That is appalling, but it gets worse, for in some parts of the world, population projections are having to be redrawn to take into account the negative effect of millions of projected AIDS deaths in upcoming decades. Of the populations that do survive, a dreadful number will be AIDS orphans. We should care about that. Despite attitudes to the contrary, Americans are not another species, and those demographic dynamics are pertinent to us. Indeed, these are dreadful, historic times! And yet, despite our resource-intensive health care system, we Americans are not using what we know. In fact, we are acting as if we do not have a problem.

With the most awesome epidemic of this century in full sway, the word one hears people say most often is "enough." "AIDS is just one disease, after all . . . haven't we done enough?" or "We've put enough into AIDS research—it is time to invest elsewhere." Or "Those AIDS activists have been entirely too effective for their cause—enough already!" I am always amused to hear people talk about the "powerful AIDS lobby" because—to a large extent—here she is. But the rest of that, to my ear, is another way of saying, "This has nothing to do with me or mine—it is those others," with the clear inference that those others are expendable. The first polio vaccine success came in 1955, after frightening years in which at most 50,000 cases of paralytic polio occurred in the worst summer. There were over 45,000 new cases of AIDS diagnosed last year! Can you imagine someone saying in 1952 that polio was just one disease and we had done enough?

Some of this comes from the layer of psychic insulation we seem to have developed around the fact that 37 million Americans lack basic health care. In Los Angeles County, a recent study revealed, 1.3 million people had been turned away when they sought health care in 1991. We should be shouting with outrage or convening urgent task forces to deal with such a shocking failure of our system. It is difficult to reconcile such startling default with the oft-stated American ideal of valuing each individual life. We are in the sole company of South Africa (among developed nations) in our failure to guarantee access to health care as a human right. Our patchwork "system" of health care is really no system at all but, rather, an entrepreneurial enterprise run amok. Almost no one is happy with it now, however advantaged; and the AIDS and drug epidemics have pressed so hard on its flawed fabric that ragged holes are gaping for all to see.

Here again, there is much we could be doing. A fringe benefit of epidemic effort over the past decade has been the innovation of cost-effective strategies to support people living with HIV or AIDS while reducing the number of hospital admissions. Outpatient care, home care, communal living arrangements in sheltered environments, and hospice alternatives all ease the costly drain on tertiary care hospitals; what is more, such alternatives can enhance and extend the quality of life. This alternative care is directly relevant to elderly and chronically ill patients and deserves amplification and support. But the deployment of such strategies has been left, to a large extent, to volunteers and community-based organizations that lack dependable resources to assure continuity. As a result, implementation has been spotty, and the remarkably dedicated people who have created these

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strategies frequently suffer burnout as a consequence of such lack of support.

And, of course, there is that other epidemic out there—so closely related to the spread of AIDS that we have coined phrases and talked about the twin epidemics of substance abuse and HIV, which in their most virulent form are Siamese twins. Whereas the sexual spread of HIV is relatively inefficient, injection drug use or crack cocaine-associated hypersexuality enhances the efficiency of transmission dramatically. Users know that and want "out," but here is a really shocking fact of American life—people who are addicted to injection drugs or crack cocaine but who want desperately to get out of the path of this awful virus cannot get treatment for their addiction if they are poor, despite a declared "war on drugs." And we are still arguing about needle access on the grounds that it "might seem to condone." Just look what we have condoned instead!

Tuberculosis is back with a vengeance. Why should that be a surprise? It was never gone, of course, just contained, like most of the other microbial pathogens we have tried to forget. Our policies have helped it rise like a phoenix from the ashes. And what a vicious creature that phoenix is, for now tuberculosis has a new, fertile substrate in people with HIV. In the complacency of recent decades, the budget slots were eliminated that should have provided the public health personnel needed to assure compliance with the long, tedious treatment necessary for eradication. Voila! Multidrug-resistant tuberculosis! We knew from our science that it had to happen, and we were correct. Where in the world do we think we are going, learning so many valid and important things and then ignoring what we know?

Science in the Era of AIDS

The Amsterdam conference in the summer of 1992 was a gathering of 10,000 hard-working persons dedicated to furthering the knowledge of effective AIDS care, HIV prevention, and fundamental science (no breakthroughs). It was also a striking sociologic phenomenon. Through diligence and special effort to include involved communities of all sorts, scientists and physicians found themselves in the company of activists and parascientific healers, sex workers and mimes, exotic ethnic dancers and dignified politicians—and from all corners of the earth. The result was kaleidoscopic, occasionally bewildering, and sometimes overwhelming.

AIDS, what an enemy! Transmitted by sex—one of the most biologically urgent and universal of human behaviors—and harbored for long, silent years by unsuspecting human accomplices whose expressions of love or lust carry occasionally lethal portent for the objects of their desire. It is not so hard, after all, to imagine how HIV survived—as it is thought to have done—for centuries in isolated human enclaves. With vertical transmission, long latency, and early sexuality, biologic survival could be maintained in families far too small to have sustained more flamboyant pathogens such as measles. A lethal virus that spreads through sexual transmission is a microbial assault weapon of awesome power—a worthy messenger of apocalyptic change.

We were at least partially prepared. I have often tried to imagine what would have happened had we not had a cushion of at least three decades of intensive investment in basic science to fall back on when AIDS surfaced in 1981. We are a generation of physicians and scientists who have been both blessed and cursed: blessed with scientific advance in the nick of time to enable us to understand the most dramatic, novel epidemic of our century, but cursed by the discontinuities and contradictions in our science and society that have threatened to render those insights ineffectual.

On the happy side, look what has been accomplished. We know a great deal about the pathogenesis of a complex retrovirus whose very existence was not suspected a decade ago. We are even clever enough to appreciate—if not yet to combat—the molecular sophistication of our adversary with its chameleon shifting of both antigenic and cytopathic properties.

We know lots more about the human immune system, too. The intricate circuitry of humoral and cellular immunity has been diagrammed, and the variety of immunologically active cells and of modulating interleukins has begun to rival the coagulation system in its rich complexity.

All of the advances have not just been analytic: we are learning how to care for people with HIV, to prevent infections and complications, and to extend a useful life of high quality for young adults whose years of potential life have been cut drastically short because they were unknowingly caught in the path of the silent, lurking virus of AIDS. Because of the pathogenetic intricacies of HIV, it has never seemed particularly rational to talk about a cure for AIDS, but it is clearly reasonable to try to extend years of productive life.

Vaccine work has been unpromising. Even partially effective vaccines for prevention are years away from general usefulness, and their evaluation and trials pose monumental problems—particularly because we already know what we need to know to avoid the virus a vaccine would be designed to prevent. Ethically we would be obligated to subvert the very substrate of efficacy trials by simple education for avoidance.

What is more, the developed world was served notice last summer in Amsterdam that populations appropriate for vaccine trial in Uganda would need to be assured access to current treatments and future vaccines on a quid pro quo basis, which is eminently reasonable but unprecedented. Even if we eventually master those logistic and ethical conundrums, a vaccine would only supplant—not replace—what we must do now, which is to confront and deal with the behaviors that put people at risk: thoughtless sex and injection drug use.

So while the news from the science front is fundamentally upbeat and exciting, there are sharp limitations to its usefulness. Given the enormous scale of the pandemic, we must be frank about what really needs doing—the first step to solving a problem is to see it clearly.

Before turning to medicine, I need to comment on some science we have not been doing. I am referring to social and behavioral science and the many facets of HIV and AIDS that are dependent on their advances. Nowhere is our lack of insight into behavioral determinants and interventions more striking than in the area of sexuality. We knew even before AIDS that we were undergoing a ferocious epidemic of other sexually transmitted diseases. And along with the escalation of infection with our new lethal pathogen have soared other kinds of trouble: the highest rate of teenaged pregnancy in the industrialized world, the highest rate of abortion anywhere that bespeaks a lack of information about and access to methods of pregnancy prevention, and other indicators of hope-

lessness such as drug use and violence that blight a whole generation of poor children in our troubled cities.

So there is much work to do, especially for our children. Yet, we have actually been blocked in efforts to do even the most carefully designed, peer-reviewed studies to describe current patterns of sexual behavior in the United States. Do you realize we are basing much of our strategic planning to deal with the most lethal sexually transmitted disease in history on the conclusions of Alfred Kinsey's study of the sexual behavior of a few thousand middle-class white men in Philadelphia? I hope they got it right back then, but who knows how it relates to today?

Let me go back to the Amsterdam conference, for a number of the themes I have been developing were illustrated by the most intensely covered "happening" there. My thoughts were jogged about our progress and problems when the press began its feeding frenzy over rumors of a "new virus." As it has turned out, there is no evidence of a new virus or even a new syndrome, but I would be willing to bet that anyone who is reminded of the Amsterdam meeting thinks about a "new virus" and wonders vaguely where that stands. Was it a new virus? What threat did it pose to public health? Finally—and this was an insistent question—In what way was this different from 1979? Were we on the brink of yet another outbreak of something new? These questions proved to be useful for achieving some perspective on these past incredibly turbulent years. The brief answer is that the few HIV-negative cases of immunodeficiency differed in virtually every way. These persons were said to be "just like AIDS patients" but lacked any evidence of HIV infection. Actually, they were not like AIDS patients. They lacked almost any unifying feature except for a low CD4 count. As the pursuit began, however, it sounded exciting. Even though there were few such patients, they were not clustered in time, and their suggestive clustering in place was more illusory than real because they had been referred to a few AIDS clinicians. We had learned so much about epidemic dynamics in all their complexity and were so sensitized to the potential importance of small clues that we were beginning to focus on dots on the television screen rather than on the big picture.

As it turned out, the "new virus" did not materialize. What seemed to reverse transcriptase activity in some tissue cultures belonged mostly to a mycoplasma—as a sadder-but-wiser virologist, let me assure you that that happens. What is more, the patients turned out not to have a "syndrome." In fact, other than low CD4 counts, they had little in common. And the blood supply issue, which had been raised instantly by the press—through clang association with events of the earlier era—was not an emergent cause for alarm. Whereas four of the patients had received blood transfusions at one point in their lives, successful follow-up of one of them found all three donors to have normal CD4 cells. Finally, analysis of HIV-negative intravenous drug users—reliable sentinels of blood-borne pathogens—showed normal CD4 cells as well. So there was no reason to raise alarms, and certainly not about the blood supply.

As the dust began to settle, the "feeding frenzy" element became clearer. In fact, the whole experience served as a reminder that there is too little distinction drawn between attention and alarm. It is thoroughly appropriate to be attentive and vigilant, for a day will come when another new pathogen surfaces. Before then, however, I hope we can learn to combine good judgment with our fancy technologies so that a sense of proportion prevails.

Medicine

Over the same decades in which virology, immunology, molecular biology, and pharmacology were racing along, medicine, too, underwent several kinds of remarkable transformations—some good and some not so good.

I will not go into detail about the technologic advances. Suffice it to say that the capacity to heal underwent several quantum leaps. Antibiotics, surgical procedures, and sophisticated diagnostic tools softened the shrouded image of hospitals as places where people went only to die. But much of our progress is coming more from pathogenetic understanding than from intervention, and a too-narrow appreciation of the source of our good fortune sets us up for trouble. Penicillin therapy does still work for syphilis, but prevention works better. We may be on the verge of a medical cure for ulcers, but alcohol still plays a role in 40% of internal medicine admissions. Birth defects from congenital rubella are nearly a thing of the past, but the effect of fetal alcohol syndrome is still being measured. Chemotherapy is offering intermittent cures and frequent surcease from dreaded cancers, but lung cancer is surging anyway, for the carcinogen still glows among us.

And then there is AIDS. It is common for people to ascribe the extension of useful life after a diagnosis of AIDS to the advent of AZT [acyclovir], but some argue that the prevention of *Pneumocystis carinii* pneumonia accounts for most of those added months and years. Other drugs have been moved into play for cytomegalovirus retinitis, for cryptococcal meningitis, even for *Mycobacterium avium-intracellulare,* but their development has seemed slow and their side effects threaten the quality of the months they help to buy. For those persons who have survived several years after diagnosis, the specter of lymphoma is now hanging over them. So therapeutic activism clearly has its limits even in fully developed AIDS.

The most sobering thing of all is the finding that—in what seems like a process of mass delusion or hysteria—large numbers of freshly graduated physicians admit to trying to pick their site of postdegree training based on where AIDS is not. That finding astonishes me, for there is no county in this land or country in this world where one can be sure of freedom from HIV. Real risks to health care professionals lie elsewhere. In 1987, of the 400 or so workplace-related deaths among 4 million health care workers in the United States, more than 200 were from hepatitis B and its complications, 19 were from electrocution, and none had anything to do with HIV. With universal precautions and hepatitis B vaccine, the health care workplace is safer than it has ever been—and the fear of HIV should give way to a committed implementation of universal precautions.

But beyond that misconceived issue of safety, why would one want to avoid participation in the epidemic of our time? I am afraid—getting back at last to metaphor—that it is because people have accepted the assertion that AIDS is God's punishment—God is punishing particularly bad people; those who get AIDS are the wrong sort, the throwaway people who are getting what they deserve. In grudging acknowledgment that there is something wrong with that sweeping condemnation, throughout these awful years one has heard

the phrase "innocent victim" with the clear imputation that the rest are guilty.

Yet, I know of no one who has gotten this virus on purpose. In contrast to people with a number of other diseases for which behavioral risks have long been recognized, the many dying now of AIDS were infected before it was even known that there was a virus "out there." The warnings we have tried to shout in more recent years have been rendered inaudible or incomprehensible through the static of mass denial—nowhere more typically than in a medical profession that still pretends it can hide.

That metaphor—of AIDS as God's punishment—brings me to the end of this soliloquy. Some years ago Susan Sontag pointed out how powerfully linked metaphor and illness could be.[1] A corollary is that evocative language can take on a pernicious and evil power if the wrong metaphor is chosen—we are liable to be captives of our own phrases and must be careful how we speak. After all, if we were truly to accept AIDS as God's punishment, should we not also deal with people with lung cancer as victims deserving of their fate? Should we not walk away from an accident victim who did not wear a seat belt? We will be learning much more about behavioral components to disease causation—and that trend would be ominous indeed if blame were to be partner to such understanding.

I contend that we have misunderstood the metaphor. If, indeed, we perceive AIDS as God's punishment, it is we who will be punished if we fail to rise to the challenge. We have raced forward with the intelligence to promote understanding and the talent to create technologies that not only allow us to intercede medically but that carry with them the obligation to care. After all, there is another metaphor at least as powerful that says we now live in a global village. Villages are busy, interconnected places where no one gets to remain a stranger. The whole world is pertinent to each of us now as never before. The AIDS epidemic reminds us—with its pandemic circling of the globe and its insistent reminder of universal sexuality, cultural denial, and adolescent risk taking—that we have more in common with our neighbors than we would once admit.

At the heart of both metaphors—the pernicious version of God's punishment of guilty persons and the positive one of a global village with all the interdependence that implies—is the issue of "others." In her lovely, eloquent speech to the 1992 Republican National Convention, Mary Fisher finally gave voice to Pastor Niemoeller's sad reflection from the days of the Holocaust:

> They came after the Jews and I was not a Jew, so I did not protest. They came after the trade unionists, and I was not a trade unionist, so I did not protest. Then they came after the Roman Catholics, and I was not a Roman Catholic, so I did not protest. Then they came after me, and there was no one left to protest.

From the same era, Charles Schoenbrunn brought forth a remembrance of his entry, as a reporter traveling with Patton's army, into one of the first concentration camps to be liberated. He tried to describe the horror of what he saw but abandoned the effort with a profound expression of inadequacy. Then he mused on how people could have been silent when such things were happening nearby. He discarded the possibility that they might not have known; the town was too close and the reek from the ovens too foul and pervasive. Finally he concluded that they must have found a way to put it out of mind because it was happening to others, and he commented that "it will only be when men and women learn to the very depths of their souls that there are no others that they will be saved from their own extinction."

We in the health professions are partway along a glorious road. The 20th century has yielded many biologic secrets of importance to the future of the human family, but only some of them come from the biomedical laboratory. Even those that do can be of use only if we recognize that we must learn to respect one another, to value prevention above intervention, however technologically dazzling, and, above all, to care. It is our privilege to be health professionals, and we must learn to know to the depths of our souls that there are no others.

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Overwhelming Postsplenectomy Infection

To the Editor: In the article on overwhelming postsplenectomy infection in the October issue,[1] Dr Malcolm Brigden describes the fatal illness of a 36-year-old man who had gone to work at 6 AM with no symptoms, returned home at 1:30 PM with malaise and myalgia, and presented to an emergency department at 6:30 PM hypotensive (80/40 mm of mercury) and febrile (40°C) with ecchymoses and petechiae. At age 5 his spleen had been removed because of hereditary spherocytosis. "A tentative diagnosis of septic shock due to postsplenectomy infection was made. Vigorous treatment with hydration, large doses of penicillin, steroids, a dopamine infusion and blood component therapy was promptly instituted. Despite these therapeutic measures, the patient died three hours after hospital admission." All antemortem blood cultures subsequently showed *Streptococcus pneumoniae.*

We are not certain of the role of the spleen in protecting against overwhelming pneumococcal bacteremia, but the spleen's function as a phagocytic line filter has been known since the 19th century.[2(p126)] In the absence of the spleen, phagocytic function remains widely dispersed in other parts of the reticuloendothelial system. A special contribution of splenic phagocytosis, however, is implicit in the postsplenectomy cure of hereditary spherocytosis and immune thrombocytopenic purpura and in protection against fatal anemia in bartonellosis.

If an asplenic person is to survive pneumococcal bacteremia, the remnant phagocytic capability of the reticuloendothelial system should not be compromised. It is well known that phagocytes are inhibited by high-dose corticosteroid therapy.[3(p1875)] The administration of "large doses" of steroids may injure asplenic patients who have overwhelming postsplenectomy infection.

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* * *

Dr Brigden Responds

To the Editor: Dr Crosby's comments regarding possible harmful effects of steroid therapy in the treatment of overwhelming postsplenectomy infection deserve careful consideration. Several recent controlled studies have questioned the efficacy and safety of steroids in treating septic shock.[1-3] In at least one review it was concluded that there is no indication for high-dose steroids in the management of this condition.[4] This position has not been universally accepted, however. For instance, a recent summary of the accumulated data indicated that high-dose corticosteroids given as one single dose during the initial hours of gram-negative septic shock more likely than not extended a beneficial effect on mortality.[5] As Dr Crosby points out, patients with overwhelming postsplenectomy infection should theoretically be more sensitive to the adverse effects of steroid therapy on phagocytic function. On the other hand, most of these patients at autopsy have shown bilateral adrenal necrosis characteristic of the Waterhouse-Friderichsen syndrome. Perhaps the correct approach lies with individualized therapy incorporating particular attention to steroid therapy later as clinically indicated.[6,7]

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* * *

To the Editor: I enjoyed the editorial by Dr Styrt[1] that accompanied my article on overwhelming postsplenectomy infection.[2] I would like to amplify her commentary in two areas: the potential value of the detection of Howell-Jolly bodies in identifying hyposplenic or functionally hyposplenic persons and the usefulness of antipneumococcal vaccination in these patients.

Dr Styrt pointed out that Howell-Jolly bodies are not pathognomonic for hyposplenism and that in certain conditions such as sprue, their presence is not always correlated to the severity of the illness. While it is true that they are not pathognomonic for hyposplenism, the cause of other hematologic conditions with which they may be associated will usually be readily apparent from other changes in the hematologic picture. Detecting persistent unexplained Howell-Jolly bodies on the peripheral blood film is an excellent marker of a degree of hyposplenism sufficient to be a risk factor for overwhelming postsplenectomy infection.[3] Persistent unexplained Howell-Jolly bodies on peripheral blood film may be investigated by algorithm (Figure 1).

If workup of a patient with Howell-Jolly bodies ultimately reveals a condition such as celiac disease, systemic lupus, or inflammatory bowel disease where hyposplenism may be transient or reversible with therapy, only counseling coupled with follow-up may be appropriate. There exist at least 11 well-documented cases of fulminant sepsis in functionally hyposplenic persons, however.[4] These patients' septicemia occurred in association with a wide variety of clinical disorders including ulcerative colitis, systemic lupus, Still's disease, sarcoidosis, following splenic irradiation, and after the administration of Thorotrast [a colloidal preparation of thorium dioxide].[4] I suspect that there have been many additional deaths in patients with hyposplenism that simply have never been reported in the literature. Despite the fact that

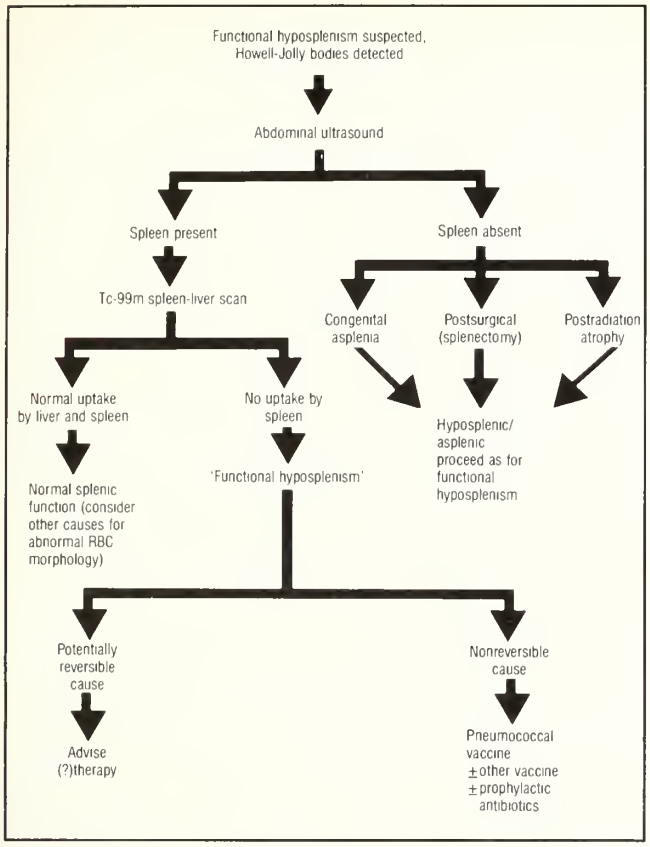

Figure 1.—A course of investigation is shown after persistent unexplained Howell-Jolly bodies are detected. RBC = red blood cell, Tc-99m = technetium 99m

there have been no specific vaccine trials in these patients, most authorities recommend that when persons with functional hyposplenism are identified, they receive antipneumococcal prophylaxis; the vaccine is both inexpensive and well tolerated.[4,5]

Patients who persistently show Howell-Jolly bodies on a peripheral blood film should always be observed to rule out functional hyposplenism. When the hyposplenism is nonreversible, they should receive the pneumococcal vaccine and other appropriate follow-up measures.

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* * *

Dr Styrt Responds

To the Editor: Information on specific data supporting steps in Dr Brigden's proposed flow chart would, I am sure, be of great assistance in the counseling of specific patients because one of the problems in clinical management is the difficulty of making predictions in a particular patient. For example, the article by Corazza and co-workers does not give any information on the actual incidence of infection,[1] and individual case reports do not provide a relative risk estimate, especially when compared with sporadic cases of overwhelming pneumococcal sepsis in persons without any known risk of hyposplenism.[2] The updated 1991 Centers for Disease Control recommendations did, as cited in my editorial, suggest both meningococcal and pneumococcal vaccine (plus possible consideration of *Haemophilus influenzae* vaccine) for adults "with splenic dysfunction or anatomic asplenia."[3] It would be interesting to know whether the potentially narrower use recommended in Dr Brigden's guidelines might result from any unanticipated differences in recommendations between countries. Because studies of pneumococcal vaccine in "high risk" populations have produced highly variable estimates of efficacy or lack thereof,[4-8] it is particularly important that using this vaccine should not induce a false sense of security leading to delayed treatment of patients known to be asplenic or hyposplenic with febrile illnesses that could represent early sepsis. Perhaps projected efforts to develop more effective pneumococcal vaccines for young children[9] might also offer new benefits for adults with hyposplenism.

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Peer Review and 'Beasom's Principle'

To the Editor: In their article, "Simultaneous Reconstruction of the Abdominal Aorta and Cholecystectomy—A Peer Review Perspective,"[1] Drs Heydorn and Moncrief observe, ". . . unfortunately some physicians are not receptive to constructive criticism from their peers."

Physicians are socialized during training to believe they must always make the right decisions for their patients and convey those decisions with an air of authority and certainty that will instill confidence in the patient, the staff, and, not least, the physician. As a result it is difficult for many physicians to admit to themselves that they have erred and nearly impossible to admit the same to others. Add to this the fact that it is unclear whether California Medical Review, Inc, reviews are protected from use by plaintiffs in lawsuits, and it is understandable and predictable that physicians are unwilling to admit clinical errors.

Years ago, after several unsatisfactory experiences counseling staff physicians at a private hospital, I received the following advice from Dr Ralph Beasom, a general surgeon and a wise man:

When you have to counsel doctors about their behavior, they will defend what they did. They will insist that they were right and that you are wrong to criticize them. You will come away from the encounter frustrated, convinced you have wasted your time. When this happens, you should not pay so much attention to what physicians *say* but rather observe what they subsequently *do*. Nine times out of ten they will correct the problem and will stop doing whatever it was that you had to counsel them about.

Over the years my experience has confirmed "Beasom's Principle." It has given me comfort to understand that counseling physicians is perhaps not the sisyphean exercise it seems. I commend the principle to Drs Heydorn and Moncrief and to all others who must counsel physicians.

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REFERENCE

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Riding, Colliding, Criminalizing—Safety and Motorcycle Helmet Laws

To the Editor: Murdock and Waxman gathered data from persons admitted to a level I trauma center and found that ". . . when riders not wearing helmets were brought to our trauma center after accidents, they had increased risks of serious head and facial injuries, prolonged hospital stays requiring ventilatory support, and either died of head injuries or were discharged with a neurologic deficit."[1] These data show, they claim, "the need for . . . mandatory helmet use legislation." But their argument contains flaws.

Why is it that some motorcyclists prefer to not wear a helmet? One reason cited by many cyclists centers on safety. Helmets impair hearing; when wearing a helmet, it is difficult to determine the location and relative motion of sounds. But accurately identifying sounds is sometimes essential to safety. Wailing sirens, screeching tires, blaring horns—even human shouts—can be warnings of danger; some warnings that are accurately understood can be heeded. The helmetless cyclist will be able to identify and evade dangers that the helmeted cyclist cannot, and the ability to avoid danger is enhanced by the inherent agility of motorcycles. Thus, declining to wear a helmet can lower the probability that a cyclist will become involved in a collision (A. Heard, "Hog-rolling," *The New Republic,* November 20, 1989, p 11).

The only persons scrutinized by Murdock and Waxman were those who had in fact been involved in motorcycle collisions. What their data show is that if one is, in fact, involved in an accident, then one is less likely to be injured, or is likely to be less seriously injured, if one is wearing a helmet. But that is the most their data can show. They show that it is safer to wear a helmet when colliding; the data do not and cannot show that it is safer to wear a helmet when riding—given that helmetlessness raises the probability of avoiding collisions.

Thus, the cyclist is confronted with two different sets of risks: wearing a helmet and increasing the probability of becoming involved in an accident but also decreasing the probability of death or the seriousness of injury in the event of an accident; or not wearing a helmet, decreasing the probability of becoming involved in an accident but increasing the probability of death or more serious injury in the event of an accident.

Choosing between sets of risks is precisely the sort of action that ought to be left to competent adults. The state exceeds its moral authority when, by threatening with fines and imprisonment, it coerces motorcyclists to choose one set of risks rather than the other; this is rank paternalism.

Let us consider the argument for helmet laws if it were based upon a hypothetical helmet. Suppose that advances in materials technology made possible the construction of a motorcycle helmet that is comfortable, strong enough to reduce injuries in the event of a collision, light enough that it does not exacerbate neck injuries, and acoustically transparent so that it does not muffle or distort sounds. Unlike current helmets, there would be no safety concerns speaking against the use of such a helmet. Would a law mandating the use of this hypothetical helmet be justified? No.

A number of other reasons can be offered for declining to wear a helmet, including the pleasure of the wind through one's hair and the importance of maintaining a particular image or self-image. For some, safety is not the decisive consideration—appearance or pleasure takes precedence over personal safety. Just as it is rank paternalism to coerce a person to subject oneself to one set of risks rather than another, it would be rank paternalism for the state to coerce a person to exalt one value (safety) over others (pleasure, image, self-image)—even if the hypothetical helmet were to be developed.

It is possible that riders declining to wear a helmet will be more seriously injured in the event of a collision; it is possible that the resultant medical costs would constitute a threat to social resources. The state can be protected from this potential public harm, however, with a well-designed, mandatory insurance program. The state exceeds its moral authority if it criminalizes the refusal to wear a helmet.

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REFERENCE

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* * *

Dr Waxman Responds

To the Editor: Professor Schonsheck's letter raises several arguments against mandatory helmet use legislation. One is that helmet use may impair hearing, resulting in increased risk of accident. There are, however, no published data showing such an increased risk, and Schonsheck certainly does not provide any. We do have some evidence to the contrary. Since helmet use only protects against head injury, one would predict that more accidents would result in more non-head injuries. Since the institution of mandatory helmet use in California in January 1992, however, we have seen notably fewer injuries from motorcycle accidents at our trauma center. There is no substantiation to the contention that helmet use results in more accidents. It seems biased and unprincipled to communicate to riders that this risk of helmet use exists.

Schonsheck makes it clear in his letter that even if this risk does not exist, he would still be against helmet laws, based

upon an argument of personal freedom. While not a professor of philosophy, I do understand the difference between rights and privileges. Operating a motorcycle is a privilege; society can and should define the attendant responsibilities, which may include education and licensure, obeying the laws of the road, and using a helmet. These mandates help minimize the enormous impact and costs of devastating head injuries to riders, their families, and society. These are not moral decisions, as implied by Schonsheck. Rather, helmet use in California is a reasonable condition for the privilege of operating a motorcycle, just as are the obligations to obey the speed limit and to be sober.

I will support one suggestion Schonsheck makes: mandatory health insurance for motorcycle riders. I agree that mandatory insurance is a good idea, made even better when combined with mandatory helmet use.

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Pizza, Pepsi, and Picking Postgraduates

To the Editor: Now is the time of year when we go about the task of choosing those persons who will become our house staff in Internal Medicine. At our institution the resident selection process is, happily, a relatively painless one. House staff and faculty gather around a box of files, soft drinks, and pizzas and review the paper profiles together.

Nowhere is an applicant's personality more apparent than in the personal statement. Letters of recommendation can also be revealing. Even deans' letters, generally celebrated as masterworks of obfuscation, can be fun. We have begun a book of notable phrases.

Personal Statements

"I am 1 of 9 children. My parents practiced the rhythm method and, lucky for me, they had no rhythm."

"I have found my niche within the human body."

"I have been exposed to anesthesia since childhood."

"As a youth I was knocked unconscious by a bolt of lightening."

"When I was 8 years old, I decided to change careers midstream."

"I have almost no chance to pursue my chosen career in Ob-Gyn since there are so few places, so I am opting for my second choice—Internal Medicine." (This one inspired us to entitle our book, "Really Dumb Things to Say on an Internship Application.")

Letters of Recommendation From Faculty and Deans

"She was a conscious, hardworking student."

"This person was quite compulsive at home at night."

"His only weakness was his fund of knowledge and his ability to apply it."

"Her only weakness was in logical thinking." (This was a surgical service, so we did not know how to interpret it.)

It is remarkable that students can negotiate the obstacle course required to select a residency program. Their individuality and perseverance inspire us. We also salute the magnanimous efforts of those who are on the receiving end, who must design, implement, and carry out the yearly selection process that determines our future colleagues and friends.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

Lessons From 1950

ARTHUR H. BAZELL, MD, *San Francisco, California*

I

I was halfway through my rotating internship, assigned to the pediatric evening drop-in clinic. My resident was kind, supportive, and a good teacher. He also had something to teach.

A young woman brought in her son. She informed me, with some disdain, that he had a rash. Her annoyance was thinly veiled. As I recall, the rash was around his waist. After inspecting it, I surmised that it was the result of flea bites. Proud of having resolved the mystery of the rash, I informed the young mother of my diagnosis. "Your son has an allergic reaction to flea bites." I offered some Benadryl elixir [diphenhydramine hydrochloride] for the boy, explaining that because there was an allergic reaction to the bites, the medicine would afford him some relief. She did not share my pride. She became indignant and huffily informed me that I must be wrong. "It couldn't be fleas! If there were fleas in the house my husband would have been the one to get them."

I backed off and sought help from the resident. I explained what had happened, still sure of the diagnosis. He smiled at me as he went to see the offended lady and her flea-bitten son. He soon returned, smiling even more broadly. "Did she accept the Benadryl?" I asked. He nodded, and I asked him how he had convinced her. "I changed the diagnosis to papular urticaria," he responded.

Lesson: Be careful what you say and to whom you say it, for even the truth may be distasteful unless couched in terms acceptable to the listener. A simple statement of fact may bring antagonism. A medical diagnosis carries authority.

II

It was late one night during my busy rotating internship. One of the staff psychiatrists had admitted a psychotic woman to the medical service where I was assigned. She was to be there overnight, for reasons I have long since forgotten. Almost as soon as she arrived, chaos set in on the ward. She kept complaining bitterly that her heart had stopped, and the more the staff tried to deal with her or ignore her, the louder and more persistently she complained.

After I finished working up my other admissions, which were several and sick, I got to her. I can still picture her standing there as I walked into her room. As soon as she saw me, she energetically thumped the right side of her chest with her right fist as she announced, "Doctor! My heart has stopped!" Seeking to better her ignorance with my knowledge, I asked her what made her think her heart was on that side. She responded, simply, "I know it is." Dubious, I checked out her assertion. Sure enough, her heart was on the right. Not only was she psychotic, probably manic, but she had dextrocardia.

The lesson here is straightforward: Always listen to your patients, even when what they tell you seems unlikely, for they are sure to know things that you do not.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

JONATHAN E. RODNICK, MD
STEPHEN J. McPHEE, MD
Assistant Editors

(Bazell AH: Lessons from 1950. West J Med 1993 Mar; 158:312)

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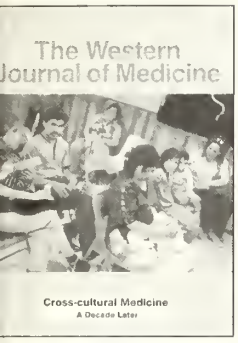

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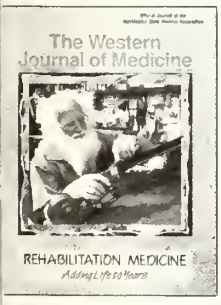

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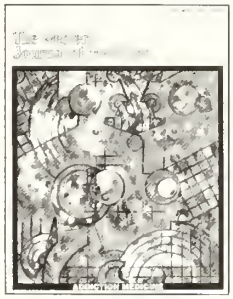

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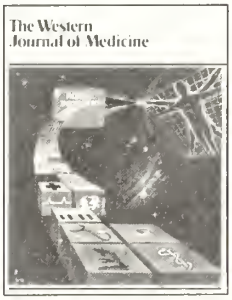

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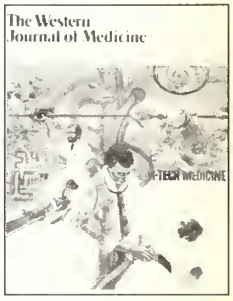

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(Continued from Page 246)

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This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

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April 2—**Nephrology and Hypertension.** UUSM at University Park Hotel, Salt Lake City. Fri. 7 hrs. $50. Contact: UUSM.

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CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
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USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 15-25—**Physical Medicine and Rehabilitation Review.** Seattle. Mon-Wed. Contact: U/W.

March 19-20—**APLS Course.** Seattle. Fri-Sat. Contact: Washington Chapter, American College of Emergency Physicians.

March 24-26—**Spirometry Training for Worker Screening.** Seattle. Wed-Fri. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

March 26-27—**Ophthalmology Annual Meeting.** Seattle. Fri-Sat. Contact: Washington Academy of Eye Physicians and Surgeons. (206) 441-9762.

March 31—**Ethics Conference.** Seattle. Wed. Contact: VMMC.

April 5-8—**Controversies and Agreements in Internal Medicine.** Maui, Hawaii. Mon-Thurs. Contact: Group Health. (206) 326-3441.

April 6-9—**Family Practice Review.** Arizona. Tues-Fri. Contact: Pacific Northwest Medical Education Institute. (206) 258-6322.

April 8-9—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

April 9—**Advances in Occupational and Environmental Medicine.** Seattle. Fri. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

April 16—**20th Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare. (206) 594-1221.

April 16-17—**Tacoma Surgical Club.** Tacoma. Thurs-Fri. Contact: PCMS CME.

April 23—**Terminal/Palliative Care Update.** Tacoma. Fri. Contact: PCMS CME.

April 23-24—**Clinical Allergy for the '90s.** Seattle. Fri-Sat. Contact: VMMC.

April 23-25—**Washington State Physical Therapy Association.** Seattle. Fri-Sun. Contact: Children's. (206) 526-2501.

April 28-30—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Fri. Contact: Washington Chapter, American College of Emergency Physicians. (206) 441-9762.

April 30-May 2—**Radiology Annual Meeting.** Vancouver, BC. Fri-Sun. Contact: Pacific Northwest Radiological Society. (206) 441-9762.

May 7—**Office Gynecology.** Tacoma. Fri. Contact: PCMS CME.

May 7-8—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

May 13—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute. (206) 258-6322.

May 14-15—**Northwest Spine Review Course.** Seattle. Fri-Sat. Contact: VMMC.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 315)

CONTINUING MEDICAL EDUCATION

(Continued from Page 314)

May 16-19—**American Thoracic Society.** San Francisco. Sun-Wed. Children's. (206) 526-2501.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare. (206) 592-1221.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

WYOMING

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆

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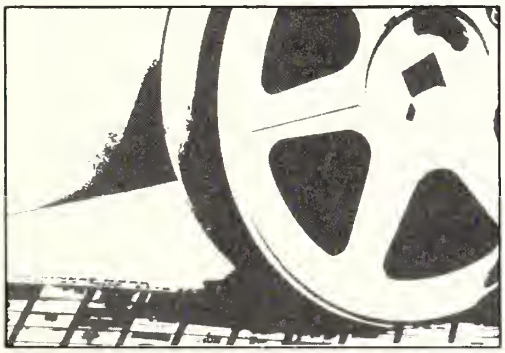

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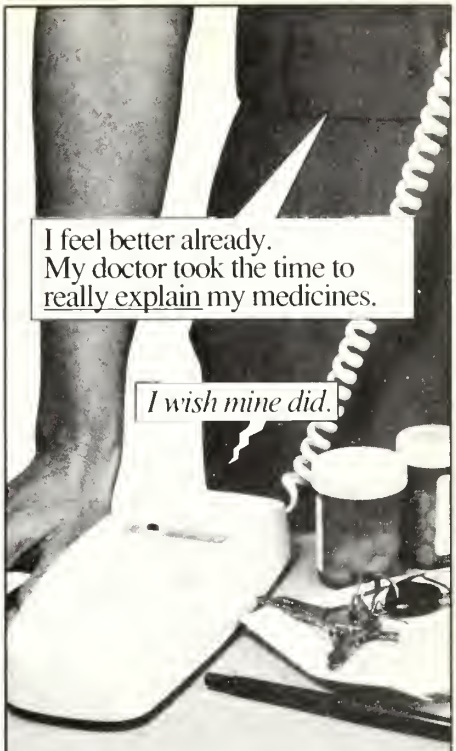

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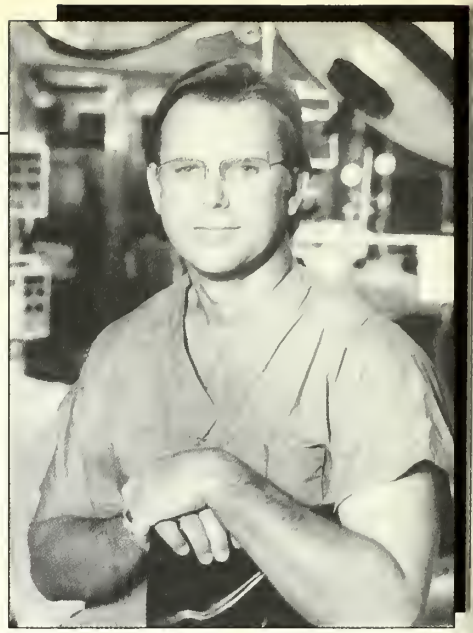

Vaughn A. Starnes, M.D. has joined the University of Southern California School of Medicine.

Vaughn A. Starnes, M.D., has joined the University o Southern California School of Medicine as Professor o Surgery, Chief of the Division of Cardiothoracic Surger and Director of the USC Cardiothoracic Center at USC University Hospital, Childrens Hospital Los Angeles and Lo Angeles County+USC Medical Center. Dr. Starnes is a world recognized leader and innovator in adult and pediatric heart heart-lung and lung transplantation and treatment of congenita heart disease.

In 1984 Dr. Starnes was accepted to the Stanford Cardiothora cic program, where he completed two years as a resident in cardio vascular surgery, and one year as chief resident in cardia transplantation under the guidance of Norman Shumway, M.D.

In 1988 Dr. Starnes was appointed director of Stanford's hear lung transplantation program, and later became chief of pediatri heart surgery and director of the transplant program at Stanford Lucile Salter Packard Childrens Hospital. He performed about 40 adult and pediatric cardiac cases annually at Stanford. In additio to his adult cardiothoracic surgical expertise, Dr. Starnes earned national reputation for his work in pediatrics.

Dr. Starnes also pioneered lung and heart-lung transplant pro cedures in children that previously had only been performed o adults. In 1991 he was the first surgeon to transplant the le upper lobe of a 2-year-old donor into a newborn with pulmona hypertension who could not be weaned off ECMO (Extracorporea Membrane Oxygenation). In 1992, he performed the first lun transplant on a baby with congenital diaphragmatic hernia.

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(Continued on Page 319)

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EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

URGENT CARE. WASHINGTON STATE. Urgent Care Center within 30 physician group seeks physician desiring practice with reasonable hours and workload. Located in the foothills of the Blue Mountains with nationally recognized liberal arts college, superb community symphony, excellent public schools, and plentiful recreational opportunities, including skiing, nearby. Guaranteed salary with incentive, excellent benefits, and retirement plans. CV to Administrator, Walla Walla Clinic, 55 W Tietan, Walla Walla, WA 99362.

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Strelcheck and Associates, Inc, an extension of our clients' recruiting departments, has positions available in Wisconsin and Michigan. We would be happy to provide you with further information. Please call (800) 243-4353 or send your CV to STRELCHECK AND ASSOCIATES, INC, 10624 N Port Washington Rd, Mequon, WI 53092.

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Well established, productive Pulmonary practice available. Heart of America—Kansas. Single tertiary hospital and office practice. 1992 net $350,000 plus. **Contact Dan L. Robison; (316) 268-8538, FAX (316) 268-8694.**

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Call (800) 727-2478 or FAX your CV in complete confidence to (408) 727-7390. Never a fee to the physician. **Nugent & Grant, 1400 Coleman Ave, Ste B24, Santa Clara, CA 95050.**

INTERNIST/FAMILY PRACTICE. Physicians for well loved multidisciplinary Geriatric health center. Part of east San Francisco bay area community clinic network. Permanent and locum tenens positions available. 50-80% time. Participation in hospital and call coverage desired. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

FAMILY PRACTICE. Seeking Family Practice or General Practice physician for rapidly growing area in northern Arizona — Bullhead City, Arizona/Laughlin, Nevada. Opportunity unlimited. Compensation unlimited. Malpractice and health insurance. Send CV to Bullhead Medical Center, 1648 Highway 95, Bullhead City, AZ 86442, or FAX to (602) 763-1311.

PUGET SOUND. BE/BC Family Practitioners to staff walk-in clinics affiliated with 100 physician multispecialty group, located 25 miles north of Seattle. Opportunity for exceptional personal and professional lifestyle. Position offers competitive salary with excellent benefits. Available winter 1992 and summer 1993. Send CV to J. G. Finley, MD, The Everett Clinic, 3901 Hoyt Ave, Everett, WA 98201.

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(Continued on Page 321)

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AIR FORCE

(Continued from Page 320)

PHYSICIANS WANTED

FAMILY PHYSICIAN–LEWISTON, IDAHO
Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson; or call (208) 743-8416.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

NORTHERN CALIFORNIA RECREATION AREA Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

CALIFORNIA–CHICO. MEDICAL DIRECTOR for busy Emergency Department with annual volume of 16,000 and growing. Successful Occupational Medicine program. The successful applicant shall be BC in Internal Medicine or Emergency Medicine, ACLS/ATLS. Guaranteed compensation with incentives. Malpractice paid. Send r sum in confidence to Administrator, Chico Community Hospital, 560 Cohasset Rd, Chico, CA 95926. FAX (916) 894-6428.

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OPPORTUNITY–URGENT CARE AND FAMILY PRACTICE. Work, live, and play within minutes of any outdoor activities you ever dreamed of. Boise offers it all including culture and an excellent atmosphere for family living. Choose 12 or 24 hour shifts. Be able to have three and four days off in a row. No on-call duties. Work at one, two, or each of our multiple facilities covering Emergency Rooms and Walk-in Family Practice. Contact Janet Meyers at (208) 466-6567 or write 1418 Caldwell Blvd, Nampa, ID 83651 to learn more about our new, exciting benefit package. (Positions also available in New Mexico.)

PHYSICIANS WANTED

MOUNTAIN VIEW. BC/BE Family Physician to join thriving four member Family Practice group located in the heart of the Silicon Valley. Practice includes Surgery and Obstetrics. C-sections are OK. Excellent salary and benefits. Contact Dianne Higgins, MD, 253 Franklin St, Mt View, CA 94041; (415) 967-5591.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524.

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

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PHYSICIANS WANTED

FAMILY PRACTICE

OREGON

NORTHWEST PERMANENTE, P.C., has an excellent full-time or half-time opportunity for a Board Certified or Eligible Family Physician to join its stable, multispecialty group, which provides care to 380,000 members of Kaiser Permanente in Oregon and Washington. The position, which is primarily general family practice and 20% urgent care, is located at our medical offices west of Portland.

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MEDICAL DIRECTOR needed in southern Arizona for medium-sized Primary Care staff model multispecialty group. BC/BE with experience as Medical Director in multicultural patient care. Successful candidate will have some of the following qualifications: in practice seven years, demonstrated management skills and have advanced degree, MHA or MPH. Call Dee Pones; (800) 658-9166, FAX CV to (602) 322-2574 or mail to CPR, PO Box 12650, Tucson, AZ 85732.

GENERAL INTERNIST in the Pacific Northwest. Busy 30 physician multispecialty group practice looking for General Internist with ICU skills and interests to join existing Internal Medicine department. Competitive salary and benefits. Send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

OREGON. BC/BE General Internist to join 21 member Internal Medicine department of 66 physician multispecialty clinic. University town. Guaranteed salary, incentive bonus, excellent benefits. Send CV to Richard M. Rytting, MD, Medical Director, The Corvallis Clinic, PC, 3680 NW Samaritan Dr, Corvallis, OR 97330.

NO HURRICANES, NO EARTHQUAKES! Just fresh air and happy living in north Idaho. An opportunity for a Primary Physician, Internist, Rheumatologist, Family Practitioner, or General Practitioner to take over an established practice at a minimal cost. Well equipped office, adjoining certified lab, experienced staff. New 170-bed hospital has state-of-the-art diagnostic and treatment facilities. Located in the foothills of the Rockies, Coeur d'Alene is a town of 25,000, a center of outdoor recreation, sports, and cultural activity. Please call Kelly at (208) 664-9234

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NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through Fall of 1994. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

EXPANDING INDUSTRIAL MEDICAL CLINIC. Physician wanted for San Francisco location. Full-time, Monday through Friday. Excellent compensation plus malpractice insurance. Send CV to The Branch Office, Box 238, 842 Folsom St, San Francisco, CA 94107.

PHYSICIANS WANTED

FAMILY PRACTICE. Premier multispecialty group near Portland, Oregon has two excellent opportunities for BC/BE Family Practitioners. Join one of two satellite clinics in which Family Physicians and Physician Assistants currently practice. Superb lifestyle, abundant recreational opportunities, and generous benefits package. Send CV to Karen Stanton, c/o The Vancouver Clinic, 700 NE 87th Ave, Vancouver, WA 98664.

PREVENTIVE MEDICINE RESIDENCY candidates sought. Two-year program includes MPH degree and practicum activities leading to BE in General Preventive Medicine. Minority candidates; those with interest in community-based health promotion/disease prevention; and candidates desiring training in public health practice in local health departments strongly encouraged to apply. Salary $31,200 plus fringes. Write, call, or FAX: Kevin Patrick, MD, MS, Director, University of California, San Diego, San Diego State University General Preventive Medicine Residency Program, San Diego, CA 92182-0567; (619) 594-5332 (phone); (619) 594-5613 (FAX).

EMERGENCY MEDICINE–FAMILY PRACTICE. California Emergency Physicians Medical Group (CEP) is a physician partnership which currently staffs 29 Emergency Departments and seven Ambulatory Care Centers throughout California. Opportunities available for physicians BC/BP in Emergency Medicine, Family Practice, Internal Medicine, and/or experienced in Primary Care. CEP offers stable contracts, excellent compensation, profit sharing, as well as health, disability, and retirement programs. For immediate consideration send CV or contact John Gravette, CEP, 2101 Webster St, #1050, Oakland, CA 94612; (800) 842-2619.

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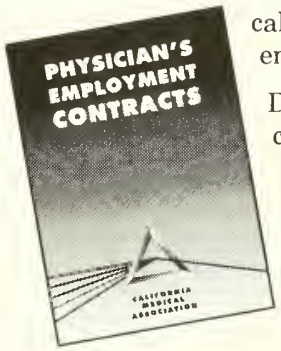
PHYSICIAN'S EMPLOYMENT CONTRACTS



CLARIFIES the laws and explains the practical issues faced by physicians negotiating employment contracts.

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WJM

(Continued from Page 322)

PHYSICIANS WANTED

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San Ramon, CA 94583
PHONE: (510) 833-0190
(800) 824-9811
FAX: (510) 833-9290

NORTHERN CALIFORNIA. Opportunities available with Comprehensive Medical Evaluations in Sacramento, San Jose, and Monterey bay area for BC physicians in Orthopedic Surgery, Psychiatry, Internal Medicine, and subspecialties, Dermatology, Neurology, Physical Medicine/Rehabilitation, Ophthalmology,Otolaryngology, Plastic/Reconstructive Surgery and Toxicology/ Occupational Medicine, to perform forensic medical evaluations. This is an excellent opportunity to supplement income without increasing your practice overhead. Send inquiry to Terence Doyle, Comprehensive Medical Evaluations, 87 Scripps Dr, Ste 308, Sacramento, CA 95825; or call (916) 567-3411.

FLORIDA GULF COAST. Two BC Hematologists/ Oncologists seeking third to join pure subspecialty practice. Competitive salary and excellent benefits. ECOG, GOG. Sophisticated medical community with a tropical climate. Send CV with cover letter to Practice Manager, 306 South Blvd, Ste B, Tampa, FL 33606.

THERE'S GREEN IN YOUR FUTURE. Thomas-Davis Medical Centers, Arizona's largest and most successful multispecialty group, needs an experienced BC/BE Internist or Med/Ped to join two others at its clinic in beautiful Green Valley, Arizona. Green Valley is located only 26 miles south of metropolitan Tucson. The retirement community of Green Valley offers picturesque views, suburban lifestyle, five golf courses, and shopping in Mexico. Top benefits, profit sharing, guarantee first two years plus incentive pay, early shareholder, and signing bonus. Call or write Dee Pones, (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732. FAX (602) 322-2676.

PUGET SOUND–WASHINGTON STATE. PEDIATRICIAN independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

PRIMARY CARE PHYSICIAN to join comprehensive health care team focused on prevention. This multidisciplinary model utilizes Day Health Centers and Home Support to keep frail elderly participants in the community active and maximally independent. Opportunity for innovation and for collaborative research with 15 similar programs. Please contact Marc Sapir, MD, The Center for Elders Independence, 1411 E 31st St, Ward B2, Oakland, CA 94602; (510) 436-7702.

(Continued on Page 324)

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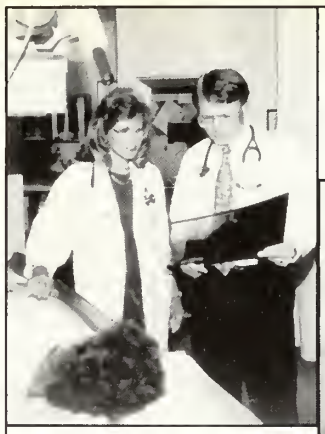

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(Continued from Page 323)

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Eight person General Internal Medicine group seeks additional physicians to join their managed care practice. 30 hour work-week, salary plus productivity, benefits, low buy-in (optional). Wanda Parker, E.G. Todd Physician Search; (800) 221-4762.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

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Pick your own Internal Medicine Practice—group, solo, partnership, hospital-based or not. Urban, suburbs, rural. Many opportunities for 93 residents. FAX CV to Medical Staffing Associates, (800) 4-FAXDOC, (800) 432-9362, or call (800) 3-MSADOC, (800) 367-2362.

BEAUTIFUL MONTEREY BAY. Immediate opportunity for a friendly, skilled, Family Practice or Emergency Physician to join highly respected Urgent Care/Occupational Medicine group with two beautiful Santa Cruz area clinics. Committed to high quality care. Nice people, flexible scheduling, comprehensive benefits, no nights, and rapid advancement to full partnership in an outstanding place to live. Please send CV to Paul Estess, Walk-In Medical Clinics, 6800 Soquel Dr, Aptos, CA 95003, or call (408) 662-3611.

PUGET SOUND–WASHINGTON STATE. RHEUMATOLOGY independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

WESTERN MONTANA. BC/BE General Internist with interest in Primary Care wanted for active 50 plus physician multispecialty group. Unparalleled outdoor recreation and outstanding schools in university town of 45,000. Income guarantee, malpractice insurance, early partnership. Excellent fringe benefits. Needed for summer/fall 1993. Send CV to Administrator, Western Montana Clinic, PO Box 7609, Missoula, MT 59807.

URGENT CARE/PRIMARY CARE PHYSICIANS. Current permanent positions available in Phoenix, Denver, Colorado Springs. Attractive settings with reasonable workload. Enticing locum tenens assignments available also throughout the Rocky Mountain west. Call or write Ed Novelli, Interim Physicians, 4155 E Jewell, Ste 1018, Denver, CO 80222; (800) 669-0718.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Maurice Montag in care of Tammie Johnson, 8009 S 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

PUGET SOUND–WASHINGTON STATE. ENT independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

PUGET SOUND–WASHINGTON STATE. OB/GYN independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

PUGET SOUND–WASHINGTON STATE. FAMILY PRACTICE independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

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LOS ANGELES, CALIFORNIA. General Practice available. Fully equipped building with x-ray, Physical Therapy, EKG, and laboratory. Building for sale or lease. Practice included. Contact Gerald Klaz, MD, PO Box 1525, Gateway Station, Culver City, CA; (213) 650-5950.

PHYSICIAN IN GENERAL PRACTICE wishes to retire. Looking for doctor to take over practice, office staff, and rent his building. Call (209) 674-4717.

FAMILY–GENERAL PRACTICE. Three miles to open staff hospital, 28 miles north of Palm Springs, California. Gross 200k per year, without hospital. No OB. Building and equipment sale or lease. Reason for sale—retiring. James S. Burrell, MD, PO Box 728, Joshua Tree, CA 92252.

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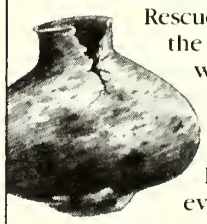

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 24-30, 1994, Marriott Hotel and Marina, San Diego.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 9-11, 1993, Ritz Carlton Kapalua, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 30-October 2, 1993, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: April 22-25, 1993, Westin La Paloma, Tucson, Arizona.

New Mexico Medical Society—7770 Jefferson, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-15, 1993, Society Office, Albuquerque.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1993, Jantzen Beach, Oregon.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 10-12, 1993, Jackson Lake Lodge, Moran.

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One Of A Kind

Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

Zantac® 150 Tablets
(ranitidine hydrochloride)
Zantac® 300 Tablets
(ranitidine hydrochloride)
Zantac® Syrup
(ranitidine hydrochloride)

BRIEF SUMMARY

The following is a brief summary only. Before prescribing, see complete prescribing information in Zantac® product labeling.

INDICATIONS AND USAGE: Zantac® is indicated in:
1. Short-term treatment of **active duodenal ulcer**. Most patients heal within 4 weeks.
2. **Maintenance therapy** for duodenal ulcer patients at reduced dosage after healing of acute ulcers.
3. The treatment of **pathological hypersecretory conditions** (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of **active, benign gastric ulcer**. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated.
5. Treatment of **gastroesophageal reflux disease (GERD)**. Symptomatic relief commonly occurs within 1 or 2 weeks after starting therapy with Zantac 150 mg b.i.d.
6. Treatment of endoscopically diagnosed **erosive esophagitis**. Healing of endoscopically diagnosed erosive esophagitis occurs at 4 weeks (47%), 8 weeks (71%), and 12 weeks (84%) of therapy with Zantac 150 mg q.i.d. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with Zantac.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer, active, benign gastric ulcer, hypersecretory states, GERD, and erosive esophagitis.

CONTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: **General**: 1. Symptomatic response to Zantac® therapy does not preclude the presence of gastric malignancy.
2. Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since Zantac is metabolized in the liver.
Laboratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac therapy, and therefore testing with sulfosalicylic acid is recommended.
Drug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that Zantac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg per day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has not been investigated.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.
Pregnancy: ***Teratogenic Effects***: ***Pregnancy Category B***: Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Nursing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children have not been established.
Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age-groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age-groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to Zantac administration.
Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.
Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.
Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.
Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred.

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

Musculoskeletal: Rare reports of arthralgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia.
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated.
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) at bedtime.
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g per day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) four times a day.
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

HOW SUPPLIED: **Zantac® 150 Tablets** (ranitidine HCl equivalent to 150 mg of ranitidine) are peach, film-coated, five-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the other. They are available in bottles of 60 (NDC 0173-0344-42) and 100 (NDC 0173-0344-09) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

Zantac® 300 Tablets (ranitidine HCl equivalent to 300 mg of ranitidine) are yellow, film-coated, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

Zantac® Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine per 1 mL in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25°C (39° and 77°F). Dispense in tight, light-resistant containers as defined in the USP/NF.

May 1992
2130A

Glaxo Pharmaceuticals
DIVISION OF GLAXO INC.

Zantac® 150 Tablets/Zantac® 300 Tablets
Glaxo Pharmaceuticals, Research Triangle Park, NC 27709

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Please see Brief Summary of Prescribing Information on adjacent page.

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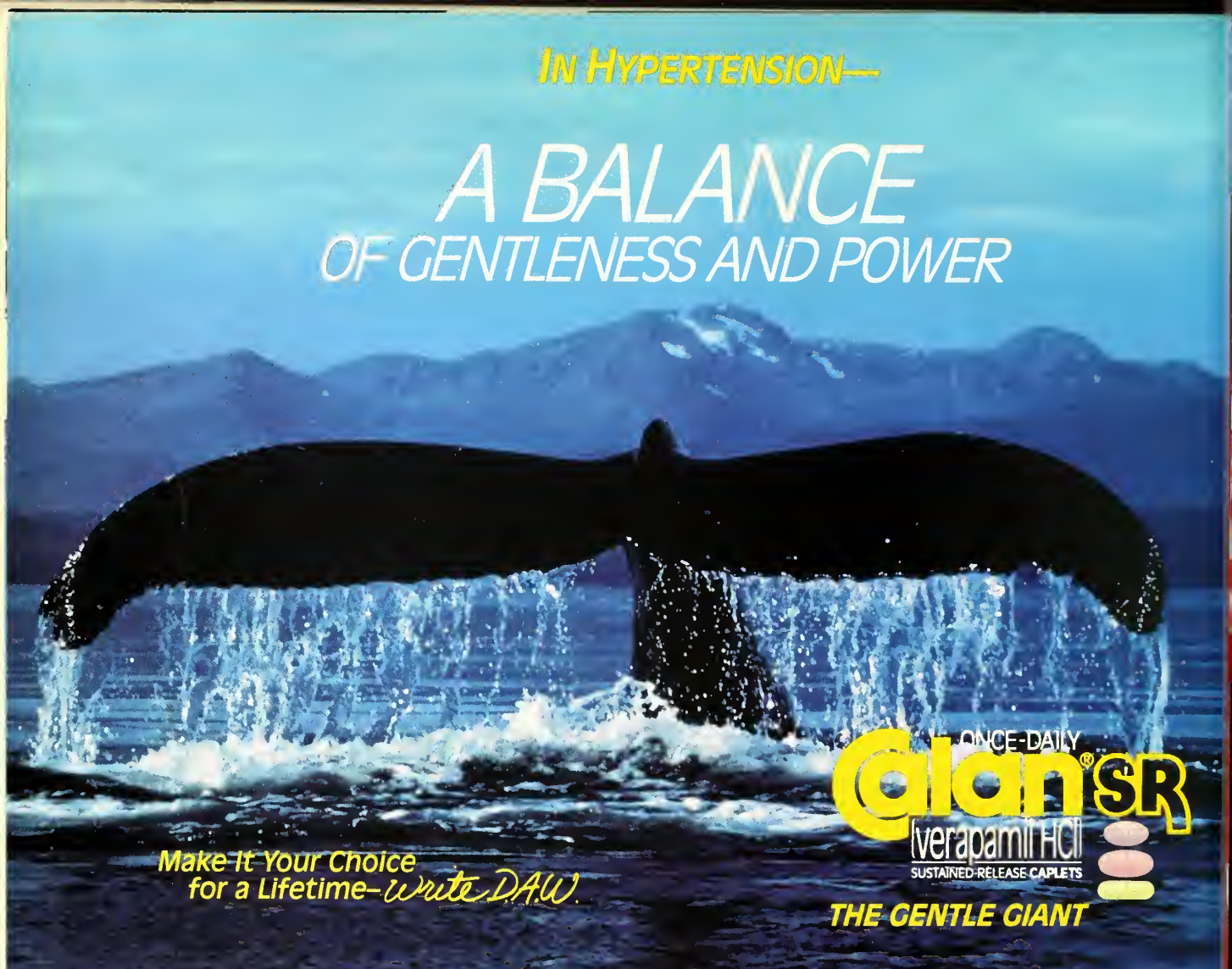

The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°, 2°, 3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, maculas, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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We report 4 cases of Trousseau's syndrome, in which spontaneous recurrent or migratory venous thromboses, arterial emboli caused by nonbacterial thrombotic endocarditis, or both, develop in a patient with a recognized or occult malignant tumor. The clinical course of 3 of the patients emphasizes a key point: The occurrence for no known reason of thromboses preventable by anticoagulation therapy with heparin but not with warfarin sodium should alert a physician to focus diagnostic efforts on uncovering an underlying malignant lesion. Thromboses may occur months to years before the tumor is discovered, and a thorough negative initial examination does not obviate the need for a continuing search. Patients with Trousseau's syndrome have persistent low-grade intravascular coagulation, and therapy with heparin should be continued indefinitely. Stopping heparin therapy for even a day may permit a new thrombosis to develop. Immunostaining a biopsy specimen from 1 patient provided evidence that 2 properties of a neoplastic lesion are required for the syndrome to develop: The malignant cells express surface membrane tissue factor, and structural features of the tumor permit the malignant cells or vesicles it sheds to be exposed to circulating blood.

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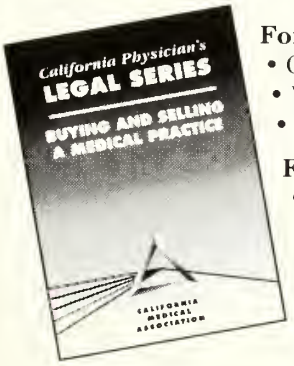

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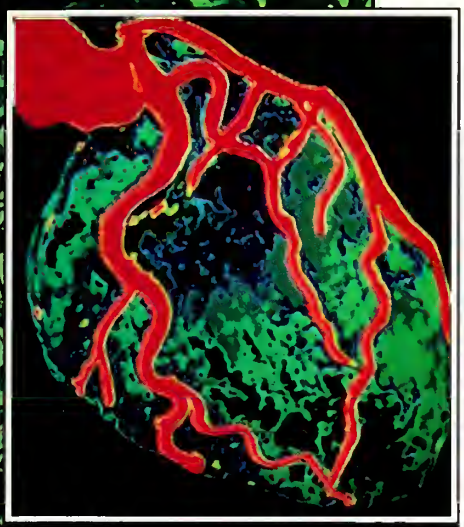

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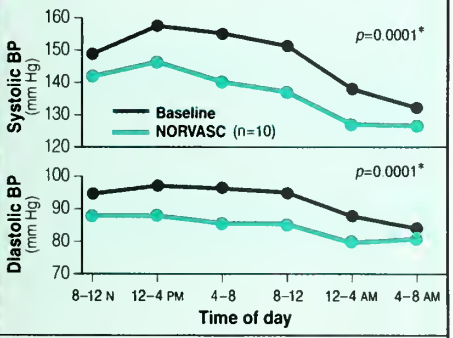

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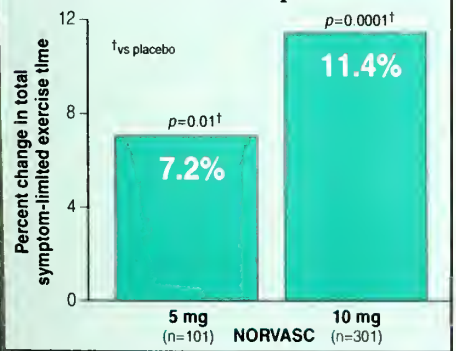

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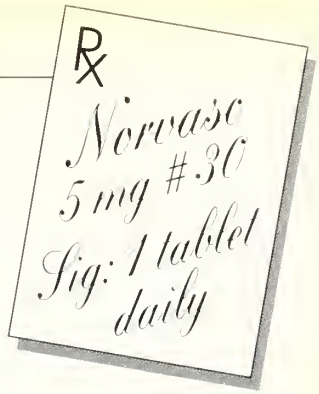

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1. Data on file. Pfizer Inc, New York, NY.

2. The Treatment of Mild Hypertension Research Group. The treatment of mild hypertension study: a randomized, placebo-controlled trial of a nutritional-hygienic regimen along with various drug monotherapies. *Arch Intern Med* 1991;151:1413-1423.

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WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase The mechanism of this effect has not been elucidated

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis

Use in Patients with Congestive Heart Failure: Although hemodynamic studies and a controlled trial in NYHA Class II-III heart failure patients have shown that NORVASC did not lead to clinical deterioration as measured by exercise tolerance, left ventricular ejection fraction, and clinical symptomatology, studies have not been performed in patients with NYHA Class IV heart failure In general, all calcium channel blockers should be used with caution in patients with heart failure

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of the beta-blocker

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life (1 ¼) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin). Special studies have indicated that the co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers, that co-administration with cimetidine did not alter the pharmacokinetics of amlodipine; and that co-administration with warfarin did not change the warfarin prothrombin response time

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1 25, and 2 5 mg/kg/day showed no evidence of carcinogenicity The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m^2 basis), was close to the maximum tolerated dose for mice but not for rats

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis)

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m^2 basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity In controlled clinical trials directly comparing NORVASC (N =1730) in doses up to 10 mg to placebo (N =1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%) The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1 1% at 2 5 mg, 3 4% at 5 0 mg, and 3 4% at 10.0 mg, compared with 1 5% placebo); flushing (0 7% at 2 5 mg, 1.4% at 5.0 mg, and 2 6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0 7% at 2.5 mg, 1 4% at 5 0 mg, and 4 5% at 10.0 mg, compared with 0 6% placebo)

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1 0% in placebo-controlled clinical trials include the following headache (7 3%, compared with 7.8% placebo), fatigue (4 5%, compared with 2 8% placebo), nausea (2.9%, compared with 1 9% placebo); abdominal pain (1.6%, compared with 0.3% placebo), and somnolence (1 4%, compared with 0.6% placebo)

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows edema (5.6% in men, 14 6% in women, compared with a placebo incidence in men of 1 4% and 5 1% in women), flushing (1.5% in men, 4 5% in women, compared with a placebo incidence of 0 3% in men and 0 9% in women), palpitations (1 4% in men, 3 3% in women, compared with a placebo incidence of 0 9% in men and 0 9% in women), and somnolence (1 3% in men, 1 6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women)

The following events occurred in ≤1% but >0 1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain, they are listed to alert the physician to a possible relationship **cardiovascular:** arrhythmia, bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, **central and peripheral nervous system:** hypoesthesia, paresthesia, tremor, vertigo, **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, vomiting **general:** asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, **musculo-skeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization, **respiratory system:** dyspnea,** epistaxis, **skin and appendages:** pruritus,** rash,** rash erythematous, rash maculopapular, **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus, **urinary system:** micturition frequency, micturition disorder, nocturia **autonomic nervous system:** dry mouth, sweating increased, **metabolic and nutritional:** thirst, **hemopoietic:** purpura

The following events occurred in ≤0 1% of patients cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia

Other reactions occurred sporadically in single patients and cannot be distinguished from concurrent disease states or medications.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, creatinine or liver function tests

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia In humans, experience with intentional overdosage of NORVASC is limited Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized, another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive, the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt, developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration A case of accidental drug overdose has been documented in a 19 month old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted Frequent blood pressure measurements are essential Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine), should be considered with attention to circulating volume and urine output Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit

* Based on patient weight of 50 kg
**These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies

More detailed professional information available on request
Revised August 1992

Pfizer Labs

ABSTRACTS APRIL 1993

(Walsh JME, Baron RB, Browner WS: Predictors of screening for hypercholesterolemia in a general internal medicine practice. West J Med 1993 Apr; 158:359-363)

We compared current practice with the National Cholesterol Education Program (NCEP) guidelines for the detection and evaluation of hypercholesterolemia and analyzed the association of various patient and provider factors with screening. Using a retrospective medical records review of 1,000 randomly selected patients between the ages of 18 and 70 in a university-based general internal medicine practice—faculty, residents (categorical and primary care), and nurse practitioners—we found that 80% of patients were screened for hypercholesterolemia. Patients older than 35 were more likely to be screened than younger patients (87% versus 77%; $P = .001$), and, among younger patients, nonwhites were less likely to be screened than whites (58% versus 77%; $P = .0001$). Lipoprotein analysis was done in 60% of the 235 patients in whom it was indicated; older patients were significantly more likely to have these measurements. Among patients taking medications for hypercholesterolemia, 92% had lipoprotein analyses done beforehand. No differences were detected in screening by provider characteristics. We conclude that providers in our practice are appropriately aggressive in screening high-risk patients for hypercholesterolemia. The finding that young whites are screened much more often than nonwhites was surprising. Finally, although there is a high rate of screening overall, many patients with elevated cholesterol levels are not appropriately classified as to their low-density-lipoprotein levels.

CHOLESTEROL
HYPERCHOLESTEROLEMIA
SCREENING FOR CHOLESTEROL LEVELS

(Walsh JME, Baron RB, Browner WS: Predictors of screening for hypercholesterolemia in a general internal medicine practice. West J Med 1993 Apr; 158:359-363)

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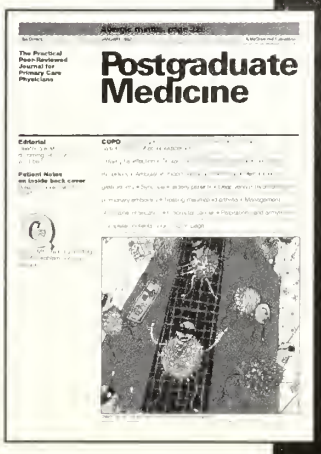

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ALLERGY/IMMUNOLOGY

May 7-8—**Asthma and Allergy in the 1990s.** American College of Emergency Physicians at Desert Inn, Las Vegas, Nevada. Fri-Sat. 10 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

September 11-12—**Case Conference in Anesthesia.** California Society of Anesthesiologists at Hyatt Hotel, Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $195. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

October 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Four Seasons Hotel, Wailea, Maui, Hawaii. Sun-Sat. 23 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

ANESTHESIOLOGY

May 20-23—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $200. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 23-28—**Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 45 hrs. $500. Contact: UCSD.

CARDIOLOGY

April 23-24—**Coronary Heart Disease Update.** American College of Emergency Physicians at Las Vegas Hilton, Nevada. Fri-Sat. 11 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

May 7-8—**Arrhythmias: Interpretation, Diagnosis and Management.** Medical Education Resources at Parc 55 Hotel, San Francisco. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

July 18-22—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

August 5-7—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 16 hrs. Contact: UCSF.

October 1-3—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

CARDIOVASCULAR DISEASE

June 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marriott Hotel, Monterey. Fri-Sun. 12 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 25-27—**Preventive Cardiovascular Medicine: Challenge for the '90s.** UCLA at Universal City Hilton and Towers, Universal City. Fri-Sun. 17.5 hrs. $175. Contact: UCLA Extension.

DERMATOLOGY

July 20-24—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation and UCSD at UCSD Campus, San Diego. Tues-Sat. 36 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-31—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $435. Contact: James Graham, MD, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 9-11—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronada. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

May 10-14—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

May 12-16—**Wound Management Workshop for Primary Care Physicians.** UCSD at San Diego Hilton Beach and Tennis Resort. Wed-Sun. 18 hrs. $475. Contact: UCSD.

June 21-25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

August 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 15-17—**Advances in Emergency Medicine.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $450. Contact: UCSD.

October 18-22—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

April 17—**Ophthalmology for Primary Care.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

April 22-24—**Rheumatology for Primary Care Physicians.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 14 hrs. Contact: UCSF.

April 22-25—**Office Orthopedics and Bone Radiology for the Primary Care Physician.** Sharp Memorial Hospital at San Diego Princess Resort. Thurs-Sun. 20 hrs. $495. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

April 23-25—**Family Practice: Today and Tomorrow.** UCSD at San Diego Hilton. Fri-Sun. 14 hrs. $150. Contact: UCSD.

May 1—**Primary Care Cardiology.** UCD at Hilton Hotel, Stockton. Sat. 6 hrs. Contact: UCD.

May 12-15—**15th Semiannual Wound Management Workshop for Primary Care.** UCSD at San Diego Hilton. 17 hrs. $475. Contact: UCSD.

May 21-22—**Chronic Renal Failure and Its Impact on Family and General Medicine.** Queen of the Valley Hospital at Clarion Hotel, Napa. Fri-Sat. $60. Contact: Becky Stephen, (707) 253-8980.

June 7-8—**Psychiatry Update for the Primary Care Physician.** University of Utah at Hyatt Regency Lake Tahoe. Mon-Tues. 9 hrs. $75. Contact: Marilyn Capener, 501 Chipeta Way, Salt Lake City, Utah 84108. (801) 584-2018.

June 10-13—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 12 hrs. $370. Contact: UCLA Extension.

June 13-18—**17th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. $495. Contact: UCD.

June 24-27—**Primary Care Sports Medicine Conference.** UCLA at Hyatt Newporter, Newport Beach. Thurs-Sat. 20 hrs. $375. Contact: UCLA Extension.

July 5-8—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

July 22-24—**Primary Care for the 21st Century.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 17 hrs. $250. Contact: UCSD.

August 6-8—**Cardiology for the Family Physician and Internist.** Continuing Medical Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

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August 20-22—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 6-9—**15th Semiannual Wound Management Workshop for Primary Care.** UCSD at San Diego Hilton. 17 hrs. $475. Contact: UCSD.

HEMATOLOGY

April 25-28—**10th Scientific Meeting of the Inter-American Society of Hypertension.** UCSD at Sheraton-Grande Torrey Pines. Sun-Wed. 39 hrs. $300. Contact: UCSD.

April 28—**World Hypertension League Symposium.** UCSD at Sheraton-Grande Torrey Pines. Wed. 4 hrs. Contact: UCSD.

May 15—**Hyperlipidemia.** UCD at Sacramento. Sat. Contact: UCD.

INFECTIOUS DISEASES

April 28-30—**Advances in Infectious Diseases.** UCSF at Sheraton Palace Hotel, San Francisco. Wed-Fri. 18 hrs. Contact: UCSF.

May 21—**7th Annual AIDS Conference: HIV at the Crossroads—The Problems and the Promises.** Alta-Bates Medical Center at Parc Oakland Hotel, Oakland. Wed. 7 hrs. $120. Contact: Carolyn Lowery or Mary Grim, (510) 204-1590.

May 24-29—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Sat. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

September 2-5—**HIV, AIDS and Women.** UCSD at La Jolla Marriott. Thurs-Sun. 15 hrs. $200. Contact: UCSD.

INTERNAL MEDICINE

May 24-28—**Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $630. Contact: UCSF.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

June 22-25—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Fri. 33 hrs. $630. Contact: UCSF.

August 22-27—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

NEUROLOGY

May 8—**Selected Topics in Neurology.** UCLA at Los Angeles Marriott. Sat. 5 hrs. $40. UCLA Extension.

May 14-16—**Neurology for the Non-Neurologist.** American College of Emergency Physicians at Doubletree Inn, Palm Springs. Fri-Sun. 12 hrs. Contact: Medical Education Resources, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756 or (303) 798-9682.

June 12-15—**Pharmacological Approaches to the Treatment of Chronic Pain: Current Concepts and Critical Issues.** UCSF at Doubletree Fisherman's Wharf, Monterey. Sat-Mon. Contact: UCSF.

August 5-7—**5th Annual New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. 14 hrs. $350. Contact: UCSD.

OB/GYN

April 14-18—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Stouffer Esmeralda Resort, Indian Wells. Wed-Sun. 22 hrs. Contact: Susan Butler, PCFS, 12760 La Mirada Blvd, Ste 220, La Mirada 90638. (310) 947-7068.

May 3-4—**The Compromised Fetus: Medical and Legal Issues.** Cedars-Sinai Med Ctr at Stouffer Esmeralda Resort, Indian Wells, Palm Desert. Mon-Tues. 7 hrs. $225. Contact: Marilyn Geary, (312) 644-6610

May 5-8—**25th Annual Meeting for the Society for Obstetric Anesthesia and Perinatology.** Cedars-Sinai Med Ctr at Stouffer Esmeralda Resort, Indian Wells, Palm Desert. Wed-Sat. 22 hrs. $350. Contact: Marilyn Geary, (312) 644-6610.

OCCUPATIONAL/ENVIRONMENTAL

July 26-30—**Sports Medicine 1993.** UCSD at San Diego Princess Resort. Mon-Fri. 21 hrs. $350. Contact: UCSD.

OPHTHALMOLOGY

May 14-15—**Pearls of Ocular Therapy.** Scripps Clinic and Research Foundation at La Jolla. Fri-Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

May 22—**Annual Research Symposium in Ophthalmology.** UCD at Cancer Auditorium, Sacramento. Sat. Contact: UCD.

ORTHOPAEDICS

May 1—**Shoulder Problems in the Throwing Athlete.** American Academy of Orthopaedic Surgeons at Sheraton Los Angeles Airport Hotel. Sat. Contact: AAOS.

May 19-22—**The Wrist: Problems and Challenges.** American Academy of Orthopaedic Surgeons at the Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: AAOS, Course Operations, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

June 3—**Problems in Spine Surgery: Complications, Controversies and Conflict.** American Academy of Orthopaedic Surgeons at Sheraton Harbor Island, San Diego. Thurs. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

June 16-19—**10th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Rebecca Rimmer, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

July 25-31—**An Update in Orthopaedics.** Kaiser Permanente at Hyatt Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $395-$495. Contact: Scott Waters, 1800 Harrison, 20th Fl, Oakland 94612. (510) 987-3087.

OTOLARYNGOLOGY

April-September 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Sun-Fri. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

June 23-25—**20th International Conference on Cochlear Implants.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. Contact: UCSF.

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SOUTHERN MEDICAL ASSOCIATION

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

MAY 14-16, 1993

THIRD ANNUAL CURRENT CONCEPTS IN ORTHOPAEDICS
LOCATION: Harbor Court Hotel, Baltimore, Maryland
SPECIALTY: Orthopaedics
CME CREDIT: CAT I-10
FEE: SMA/SOA Member-$125; Nonmember-$275; Nonphysician-$75

JUNE 4-6, 1993

THIRD ANNUAL FOCUS ON PEDIATRIC AND ADOLESCENT PATIENTS
LOCATION: Sandestin Resort and Conference Center, Destin, Florida
SPECIALTY: Primary Care, Pediatrics
CME CREDIT: CAT I-13; AAFP 12.5 Prescribed; AOA 12.5 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$195

JUNE 11-13, 1993

PHYSICAL MEDICINE AND REHABILITATION UPDATE
LOCATION: The Ritz-Carlton, Naples, Florida
SPECIALTY: Orthopaedics, PM and R, Family Practice
CME CREDIT: CAT I-15; AAFP 15 Prescribed; AOA 15 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$195

JUNE 13-17, 1993

SEVENTEENTH SYMPOSIUM ON LUNG DISEASE
LOCATION: The Cloister, Sea Island, Georgia
SPECIALTY: Pulmonary Medicine, Critical Care Medicine, Internal Medicine
CME CREDIT: CAT I-24
FEE: SMA Member-$395; Nonmember—$520; Nonphysician—$200

JULY 9-11, 1993

THIRD ANNUAL OFFICE MANAGEMENT OF INFECTIOUS DISEASES
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Gynecology, Pediatrics
CME CREDIT: CAT I-15; AAFP 15.25 Prescribed; ACOG 15 Cognates; AOA 15.5 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 19-22, 1993

SECOND ANNUAL SURGERY UPDATE
LOCATION: The Cloister, Sea Island, Georgia
SPECIALTY: General Surgery
CME CREDIT: CAT I-14
FEE: SMA Member-$400; Nonmember $525; Nonphysician-$250

JULY 26-29, 1993

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Obstetrics and Gynecology, Primary Care
CME CREDIT: CAT I-18; AAFP 18 Prescribed; ACOG 19 Cognates; AOA 18 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 30-AUGUST 1, 1993

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Urology
CME CREDIT: CAT I-14; AAFP 13 Prescribed; AOA 14 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

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EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Plastic Surgery

Items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently became reasonably firmly established, both as to scientific fact and important clinical significance.

400 **Face-lift and Blepharoplasty**
THOMAS P. WHETZEL, MD

401 **Coverage of Burn Wounds**
DEBRA A. REILLY, MD

401 **Wrist Pain**
KEVIN F. CIRESI, MD, and SUZANNE M. KERLEY, MD

402 **Cleft Lip and Palate and Craniofacial Operation**
SETH R. THALLER, MD, DMD

403 **Basal Cell Carcinoma**
TOBY R. MELTZER, MD

403 **Pressure Sores**
LAWRENCE L. KETCH, MD

404 **Laser Treatment of Skin Lesions**
THOMAS R. STEVENSON, MD

ALERTS, NOTICES, AND CASE REPORTS

406 **Peritoneal Coccidioidomycosis Diagnosed Incidentally at Herniorrhaphy**
JOSE A. PEREZ, Jr, MD, and EDWARD L. ARSURA, MD

From the Department of Medicine, Kern Medical Center, Bakersfield, California, University of California, Los Angeles, School of Medicine.

406 **Acute Renal Failure Following Intravenous Streptokinase Infusion for Acute Myocardial Infarction**
YOCHAI BIRNBAUM, MD; BORIS STRASBERG, MD; ELDAD RECHAVIA, MD; YORAM NEUMAN, MD; and BRACHA STAHL

From the Cardiac Intensive Care Unit, Departments of Cardiology and Internal Medicine A, and the Drug Information Center, Beilinson Medical Center, Petah-Tikva, and the Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel.

409 **Acute Leukemia Associated With Mediastinal Germ Cell Tumor—De Novo Versus Therapy-Related Leukemia**
YI-KONG KEUNG, MBBS; RAYMOND LIANG, MBBS, MRCP; and EDMOND K. W. CHIU, MBBS, MRCP

From the Norris Kenneth Jr Cancer Hospital and Research Institute, Division of Hematology, University of Southern California School of Medicine, Los Angeles, and the University of Hong Kong.

412 **Severe Angioedema and Respiratory Distress Associated With Lisinopril Use**
GUY W. SOO HOO, MD; HUONG T. DAO, MD; and WILLIAM B. KLAUSTERMEYER, MD

From the Allergy and Immunology Section, Pulmonary and Critical Care Section, Medical and Research Services, Department of Veterans Affairs Medical Center, Wadsworth Division, Los Angeles, California, and the University of California, Los Angeles, School of Medicine.

COMMENTARY

418 **Bedside Teaching**
FAITH T. FITZGERALD, MD

From the Department of Internal Medicine, University of California, Davis, Medical Center, Sacramento.

(Continued on Page 354)

A source of strength in a world of resistance

CEFOBID® 1g/2g q12h

(cefoperazone sodium) IM/IV

Please see adjacent page for brief summary of prescribing information

CEFOBID® (cefoperazone sodium) has maintained in vitro activity over time

- An excellent *in vitro* susceptibility profile against the most common nosocomial pathogens[1-3]

Pseudomonas aeruginosa[2,3]		*Staphylococcus aureus*[2,3]	
1985	1990	1985	1990
91.0%	93.1%	92.0%	91.3%
(n=388)	(n=15,439)	(n=369)	(n=2,554)

From a retrospective, multicenter susceptibility data base; n=number of isolates; percent susceptible calculated with 95% confidence limits.

In vitro activity does not necessarily imply a correlation with *in vivo* results.

- An established record of clinical effectiveness in nosocomial pneumonia,* in complicated UTI,* and for approved indications in the febrile neutropenic patient*[4-8]
- No dosage adjustment required for the renally impaired
- Low sodium load
- Convenient, cost-effective q12h dosing

Contraindicated in patients with known allergy to the cephalosporin class of antibiotics

CEFOBID® 1g/2g q12h (cefoperazone sodium) IM/IV

A force against resistance

*Due to susceptible strains of indicated organisms, such as *P aeruginosa*.

References. 1. Horan T, Culver D, Jarvis W et al. Pathogens causing nosocomial infections: preliminary data from the National Nosocomial Infections Surveillance System. *Antimicrobic Newsletter* 1988;5(9):65-67. **2.** Data available on request from Roerig. **3.** Jenkins SG. Comparative susceptibility patterns of common clinical isolates to cefoperazone: 1981 to 1987. *Am J Med* 1988;85(suppl 1A):52-55. **4.** Mangi RJ, Greco T, Ryan J, Thorton G, Andriole VT. Cefoperazone versus combination antibiotic therapy of hospital acquired pneumonia. *Am J Med* 1988;84:68-74. **5.** Mangi RJ, Ryan J, Berenson C et al. Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. *Am J Med* 1988;85(suppl 1A):44-48. **6.** Mangi R, Peccerillo K, Moleski RJ. Treatment of nosocomial pneumonia. Presented as an educational exhibit at the 47th Annual Meeting of the American Society of Hospital Pharmacists, June 3-7, 1990, Boston, Mass. **7.** Cohen MS, Washton HE, Barranco SF. Multicenter clinical trial of cefoperazone sodium in the United States. *Am J Med* 1984;77:35-41. **8.** Kiehl A, Greenberg RN. Treatment of febrile neutropenic patients: evaluation of antibiotic regimens with or without vancomycin. Presented at the 24th Annual ASHP Midyear Clinical Meeting, December 3-7, 1989, Atlanta, Ga.

Brief Summary

CEFOBID® (cefoperazone sodium) *For Intravenous or Intramuscular Use*

CONTRAINDICATIONS: CEFOBID (cefoperazone sodium) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics. **WARNINGS:** BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH THE USE OF CEPHALOSPORINS (AND OTHER BROAD-SPECTRUM ANTIBIOTICS), THEREFORE, IT IS IMPORTANT TO CONSIDER ITS DIAGNOSIS IN PATIENTS WHO DEVELOP DIARRHEA IN ASSOCIATION WITH ANTIBIOTIC USE. **PRECAUTIONS:** Although transient elevations of the BUN and serum creatinine have been observed, CEFOBID alone does not appear to cause significant nephrotoxicity. However, concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity.

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID is increased 2-4 fold in patients with hepatic disease and/or biliary obstruction. In general, total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored.

Because renal excretion is not the main route of elimination of CEFOBID, patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

The half-life of CEFOBID is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period. In patients with both hepatic dysfunction and significant renal disease, CEFOBID dosage should not exceed 1-2 g daily without close monitoring of serum concentrations.

As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFOBID. Those at risk include patients with a poor nutritional status, malabsorption states (e.g., cystic fibrosis), alcoholism, and patients on prolonged hyperalimentation regimens (administered either intravenously or via a nasogastric tube). Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.

A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFOBID (cefoperazone sodium) administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID. A similar reaction has been reported with other cephalosporins.

Prolonged use of CEFOBID may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.

CEFOBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. **Drug Laboratory Test Interactions:** A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range; the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically, the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown. **Usage in Pregnancy: Pregnancy Category B:** Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Usage in Nursing Mothers:** Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children have not been established. For information concerning testicular changes in prepubertal rats see Carcinogenesis, Mutagenesis, Impairment of Fertility. **ADVERSE REACTIONS:** In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID® (cefoperazone sodium) therapy or uncertain etiology. **Hypersensitivity:** As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin. **Hematology:** As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10. **Hepatic:** Of 1285 patients treated with cefoperazone in clinical trials one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms of nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pretreatment levels and the symptomatology resolved. As with other antibiotics that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5-10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established. **Gastrointestinal:** Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibiotic therapy (see WARNINGS). **Renal Function Tests:** Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted. **Local Reactions:** CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

Pfizer Roerig

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PATHOLOGY

April 17—**New Treatments in Chronic Liver Disease.** Scripps Clinic and Research Foundation at La Jolla. Sat. 6 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Blvd, La Jolla 92037. (619) 554-6310.

May 27-29—**9th Annual Current Issues in Anatomic Pathology: 1993.** UCSF at Mark Hopkins Intercontinental Hotel Nob Hill, San Francisco. Thurs-Sat. 19.5 hrs. $450. Contact: UCSF.

June 1-5—**Non-Gynecologic Cytopathology.** American Society of Clinical Pathologists at San Francisco. Tues-Sat. Contact: 2100 W Harrison St, Chicago, IL 60612-3798. (312) 738-1336.

August 7-14—**14th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Kapalua, Maui, Hawaii. 1 wk. 27 hrs. $950. Contact: UCSF.

October 2—**33rd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Stouffer Esmeralda Resort, Indian Wells. Sat. Contact: Sylvie Tarro, (310) 641-8152.

October 15-19—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

May 8—**Childhood Hearing Problems—Dx and Rx in Your Office.** O'Connor Hospital/Hearing Institute for Children and Adults at O'Connor Hospital Auditorium. Sat. 5 hrs. $35. Contact: O'Connor Hospital, 2105 Forest Ave, San Jose 95128. (408) 288-7777.

May 13-15—**26th Annual Advances and Controversies in Clinical Pediatrics.** UCSF at Fairmont Hotel, San Francisco. Thurs-Sat. 16 hrs. $325. Contact: UCSF.

June 6—**Pediatric Pathology.** California Tumor Tissue Registry at Westin Mission Hills Resort, Rancho Mirage. Sun. 8 hrs. Contact: CTTR, c/o Loma Linda School of Medicine, AH 335, Loma Linda 92350. (909) 824-4788.

June 11-13—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 14 hrs. Contact: Children's Hospital, (619) 576-4072.

July 8-12—**Lactation Educator Training Programs.** UCLA at Ramada Inn, Beverly Hills. Thurs-Mon. Contact: UCLA Extension.

August 23-25—**Pediatrics Update: 1993.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

April 24—**Somatization, Conversion, Dissociation: Diagnosis and Treatment.** Southern California Psychiatric Society at Biltmore Hotel, Los Angeles. Sat. 6 hrs. Contact: SCPS, (310) 315-7233.

April 24-25—**The Cutting Edge Conference 1993: The Treatment of Severe Personality Disorders.** UCSD at Doubletree Hotel, San Diego. Sat-Sun. 13 hrs. $325. Contact: UCSD.

April 29-May 2—**12th Annual Child Abuse Conference.** UCD at Red Lion Inn, Sacramento. Thurs-Sun. 12 hrs. $175. Contact: UCD.

May 14-19—**The Power of Art: Introduction to Medical Hypnosis.** UCSD at Colonial Inn, Del Mar. Fri-Mon. 26 hrs. $595. Contact: UCSD.

May 22—**Biofeedback, Hypnosis, and Neuro-Physiologic Response in Health and Disease.** San Francisco Academy of Hypnosis Educational and Research Foundation at Letterman Medical Center, San Francisco. Sat. $60-$100. Contact: SFAH, 615 27th St, San Francisco. (415) 282-3754.

RADIOLOGY

April 15-17—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Thurs-Sat. 20 hrs. $500. Contact: UCSD.

April 18-23—**13th Annual Residents' Radiology Review Course.** UCSD at Hotel del Coronado, San Diego. Sun-Fri. 41 hrs. $600. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 23-24—**Imaging for Clinicians.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

April 24—**Interventional Radiology.** UCSD at Hotel del Coronado, San Diego. Sat. 8.25 hrs. $135. Contact: Dawne Ryals, PO Box 1925, Roswell, GA 30077-1925. (404) 641-9773.

April 25-30—**Diagnostic Imaging in Paradise: 1993.** UCSF at Ritz-Carlton, Mauna Lani, Koni, Hawaii. Sun-Fri. 22.5 hrs. $595. Contact: UCSF.

May 3-7—**Magnetic Resonance Imaging and Ultrasound in Yosemite.** UCSF at Marriott's Tenaya Lodge, Yosemite Park. Mon-Fri. 22.5 hrs. $595. Contact: UCSF.

May 24-28—**Practical Body Imaging: CT, US, MRI in the 1990s.** UCSF at Marriott Hotel, Monterey. Mon-Fri. 21 hrs. $595. Contact: UCSF.

June 3-5—**2nd Annual Course in Interventional Hepatobiliary Radiology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17.5 hrs. $600. Contact: UCSF.

June 6-9—**Advanced Echocardiography and Doppler Ultrasound 1993.** American College of Cardiology at Hyatt Islandia, San Diego. Sun-Wed. 22.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

June 14-18—**MRI: A State-of-the-Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, San Francisco. Mon-Fri. 27 hrs. $650. Contact: STAN.

October 18-20—**Radiology and the Non-Radiologists.** UCSD at Hyatt Regency, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

RISK MANAGEMENT

April 20-21—**High Risk Emergency Medicine: Preventing Malpractice.** Kaiser Permanente Emergency Medical Group at San Francisco. Tues-Wed. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

May 5-6—**High Risk Emergency Medicine: Preventing Malpractice.** Emergency Medical Group at Palm Springs. Wed-Thurs. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

June 14-16—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at Honolulu, Hawaii. Mon-Wed. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

July 19-20—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at San Diego. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

September 27-28—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, (800) 451-7475.

SURGERY

April 15-17—**Postgraduate Course in General Surgery.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 15 hrs. $345. Contact: UCSF.

April 18-23—**Controversial Areas in General Surgery.** UCLA at Hotel Indian Wells, Indian Wells. Sun-Fri. 16 hrs. Contact: UCLA Extension.

May 20-21—**8th Annual Neurosurgery Postgraduate Course: Intracranial Tumors—Modern Management.** UCSF at Grand Hyatt on Union Square. Tues-Thurs. Contact: UCSF.

VASCULAR DISEASE

May 6-8—**4th Annual UCLA Symposium on Interventional Therapy for Vascular Disease.** UCLA at Beverly Hills Hilton. Thurs-Sat. Contact: Thomas McNamara, Discovery International, (800) 338-4721, ext. 605.

June 25-26—**Advances in Vascular Disease.** Medical Educational Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

GENERAL/MULTIDISCIPLINARY

June 11-13—**The Medical Office Laboratory Conference.** SDSU at San Diego Red Lion Hotel. Fri-Sun. 20 hrs. $425. Contact: Nancy Geiser, (619) 594-6255.

June 25—**Bioethics Conference.** UCD at Hyatt Regency, Sacramento. Fri. Contact: UCD.

October 14-17—**Women in Medicine.** UCSD at San Diego Hilton. Thurs-Sun. 15 hrs. $300. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology and Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

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Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

April 22-24—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

April 26-27—**Neonatal Resuscitation Hospital-based Instructor Course.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6668.

May 7-8—**A Caring Affair.** Children's Hospital, Denver. Fri-Sat. Contact: Angela Pollack, (303) 861-6506.

May 10-13—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6188.

June 10-11—**Basic/Advanced Fetal Monitoring Program.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Trish Beachy, (303) 270-8376.

June 10-11—**Neonatal Resuscitation Program Provider Course.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Outreach Office, (303) 861-6668.

June 10-12—**Sixth Annual Summer in the Mountains Conference.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Sat. Contact: Mary Haley, (303) 270-8376.

June 14-16—**Community Health Traineeship Program.** Children's Hospital, Denver. Mon-Wed. Contact: Outreach Office, (303) 861-6668.

July 13—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

July 30-August 1—**Second Annual Medical Ethics Conference.** University of Colorado Health Sciences Center at Aspen. Fri-Sun. Contact: Phyllis Schroeder, U of Colo.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

August 23-27—**18th Annual Musculoskeletal Care.** University of Colorado Health Sciences Center at Breckenridge. Mon-Fri. Contact: Phyllis Schroeder, U of Colo.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761

IDAHO

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 1—**New Mexico Society of Anesthesiologists Annual Meeting.** Hilton of Santa Fe. Sat. Contact: Homer Musgrave, MD, 1308 Morningside NE, Albuquerque 87110. (505) 255-5152.

May 14-15—**New Mexico Medical Society Annual Meeting.** Society Office, Albuquerque. Fri-Sat. Contact: NMMS, 7770 Jefferson NE, Ste 400, Albuquerque 87109. (505) 828-0237 or (800) 748-1596.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

July 5-9—**Update in Internal Medicine.** UUSM at Olympia Hotel and Conference Center, Park City. Mon-Fri. Contact: UUSM.

September 22-25—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

(Continued on Page 431)

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Best of pork

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Pork Top Loin Roast (boneless), trimmed	165	6.1 g	2.2 g	66 mg
Center Loin Chop, trimmed	172	6.9 g	2.5 g	70 mg
Chicken Thigh, skinless	178	9.2 g	2.6 g	81 mg

*Table refers to 3-oz, cooked servings.

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- Trim away any visible fat.
- Keep portions moderate (about 3 oz, cooked).
- Prepare by broiling or roasting, and avoid additional fat in preparation.

1. US Dept of Agriculture. *Composition of Foods: Pork Products*, 1992. Agricultural handbook 8-10.
2. US Dept of Agriculture. *Composition of Foods: Poultry Products*, 1979. Agricultural handbook 8-5.

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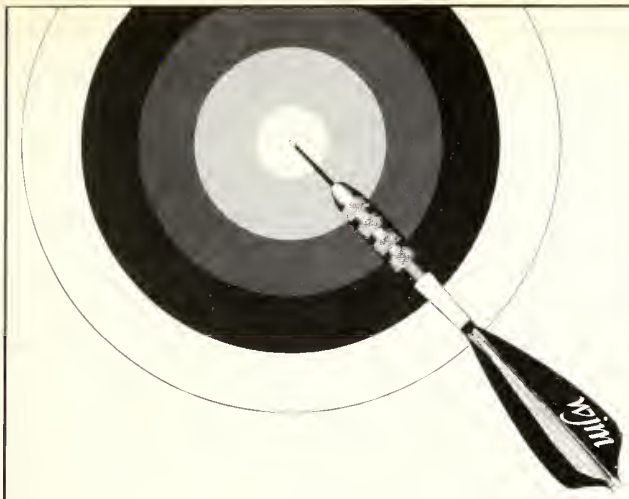

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Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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- Conferences and Reviews: 3,000 words*
- Alerts, Notices, and Case Reports: 1,500 words
- Lessons From the Practice: 1,000 words
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All manuscripts will be subject to peer review.

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FREE HIV RISK ASSESSMENT PROGRAM AVAILABLE

CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

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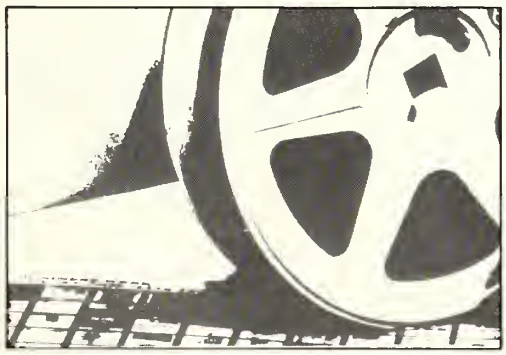

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Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below

Lower Respiratory Tract Infections caused by β lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*
Otitis Media caused by β lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*
Sinusitis caused by β lactamase producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*
Skin and Skin Structure Infections caused by β lactamase producing strains of *Staphylococcus aureus, E. coli*, and *Klebsiella* spp
Urinary Tract Infections caused by β lactamase producing strains of *E. coli, Klebsiella* spp and *Enterobacter* spp

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β lactamase producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β lactamase producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate

Contraindications: A history of allergic reactions to any penicillin is a contraindication

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY. IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS, OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an oral antibiotic drug effective against *C. difficile*

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently

Augmentin should not be co administered with Antabuse® (disulfiram)

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%)

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache

The following adverse reactions have been reported for ampicillin class antibiotics

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS)

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (See WARNINGS)

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely

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Articles

Predictors of Screening for Hypercholesterolemia in a General Internal Medicine Practice

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Presented as an abstract at the Society of General Internal Medicine Annual Meeting, Seattle, Washington, May 1991.

We compared current practice with the National Cholesterol Education Program (NCEP) guidelines for the detection and evaluation of hypercholesterolemia and analyzed the association of various patient and provider factors with screening. Using a retrospective medical records review of 1,000 randomly selected patients between the ages of 18 and 70 in a university-based general internal medicine practice—faculty, residents (categorical and primary care), and nurse practitioners—we found that 80% of patients were screened for hypercholesterolemia. Patients older than 35 were more likely to be screened than younger patients (87% versus 77%; $P=.001$), and, among younger patients, nonwhites were less likely to be screened than whites (58% versus 77%; $P=.0001$). Lipoprotein analysis was done in 60% of the 235 patients in whom it was indicated; older patients were significantly more likely to have these measurements. Among patients taking medications for hypercholesterolemia, 92% had lipoprotein analyses done beforehand. No differences were detected in screening by provider characteristics. We conclude that providers in our practice are appropriately aggressive in screening high-risk patients for hypercholesterolemia. The finding that young whites are screened much more often than nonwhites was surprising. Finally, although there is a high rate of screening overall, many patients with elevated cholesterol levels are not appropriately classified as to their low-density-lipoprotein levels.

(Walsh JME, Baron RB, Browner WS: Predictors of screening for hypercholesterolemia in a general internal medicine practice. West J Med 1993 Apr; 158:359-363)

Recommendations for the detection, evaluation, and treatment of high blood cholesterol levels have recently been published by the National Cholesterol Education Program (NCEP). These include the measurement of blood cholesterol levels in all adults, evaluation for the presence of other cardiovascular risk factors to classify persons as to high or low risk, lipoprotein analyses in all those with elevated total cholesterol levels, dietary therapy for those with elevated low-density-lipoprotein-cholesterol levels, and progression to pharmacologic therapy if dietary treatment fails.[1]*

Although considerable effort has gone into establishing the guidelines and publicizing the recommendations, little is known about the extent to which they are implemented in clinical practice. Previous research on the effects of practice guidelines concludes that they may predispose physicians to consider changing their behavior, but unless there are other incentives or the removal of disincentives, they may be "unable to effect rapid change in clinical practice."[2]

*See also "Cholesterol Awareness—Key to Preventing Coronary Artery Disease" by J. L. Witztum, MD, on pages 423-424 of this issue.

Previous studies have assessed clinicians' reported practices in screening for hypercholesterolemia. In a telephone survey of New York State primary care practitioners to assess physicians' knowledge of and adherence to NCEP guidelines, many inconsistencies were found between the NCEP recommendations and reported clinical practices.[3] Physicians' actual management practices, however, were not assessed.

The National Heart, Lung, and Blood Institute has sponsored periodic telephone surveys of practicing physicians to assess attitudes and practices related to high blood cholesterol. In the most recent of these surveys (1990), physicians self-reported that they were treating elevated blood cholesterol at significantly lower levels than they had in the past. Furthermore, more than 90% of the surveyed physicians reported an awareness of and use of the NCEP guidelines in screening for hypercholesterolemia.[4] Other studies of physicians' screening practices, however, have shown that physicians substantially overestimate their actual use of screening tests.[5]

This study was designed to compare actual practice with current NCEP recommendations for screening for

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hypercholesterolemia among clinicians in a university general internal medicine practice. We also investigated the association of patient and provider factors with screening for elevated blood cholesterol levels. Patient factors included sex, age, race, cardiovascular risk, insurance status, and number of medications. Provider factors included physician versus nurse practitioner, faculty versus resident, sex, and year of completion of training.

Patients and Methods

The study was conducted in the General Internal Medicine Group Practice at the University of California, San Francisco. Approximately 17,500 patients are cared for in the practice. The patient population is 60% white, 15% Hispanic, 15% Asian or Pacific Islander, and 10% African American. About 60% of the patients are women, and the median age is 58. Primary care providers include faculty physicians, primary care internal medicine residents, categorical program internal medicine residents, and nurse practitioners. Patients are assigned to providers as new appointment openings become available. For this study, patients being cared for by medical and nurse practitioner students were excluded.

Between November 1990 and January 1991, the medical records of 1,000 patients were reviewed by one of us (J.M.E.W.). Inclusion criteria were an age of 18 to 70 at the time of the study, the assignment of care to a permanent provider, and at least one visit to the practice since July 1988 (the NCEP guidelines were published in January 1988, and 6 months were allowed for the dissemination of the guidelines). Patients with diseases associated with a limited life expectancy (such as the acquired immunodeficiency syndrome or metastatic cancer), such that screening for elevated cholesterol levels would not be indicated, were excluded. Educational efforts to disseminate the NCEP guidelines included noontime didactic conferences for all providers and conspicuous posting of cholesterol screening algorithms in examination rooms and other areas of the clinic.

Medical records were selected by the use of random numbers. The problem list was evaluated, and patients who met the exclusion criteria were not analyzed further. Eligible records then were reviewed to ascertain the cardiovascular risk factors defined by the NCEP—male sex, hypertension, smoking, family history, diabetes mellitus, obesity, peripheral vascular disease, or cerebrovascular accident. Patients were classified as high risk if they had two or more of these risk factors or had documented manifestations of coronary artery disease. Age, sex, race, insurance status, and number of medications were also ascertained. Race was classified as white versus nonwhite (African American, Asian or Pacific Islander, Hispanic, and other). Insurance status was classified as private or self-pay versus other (Medicare, Medi-Cal, and health maintenance organizations). The number of medications was used as a simple measure of other treated medical disorders.

Providers were classified as faculty physicians (n = 15), staff nurse practitioners (n = 9), or internal medicine residents (categorical program [n = 25] and primary care [n = 12]). Providers' sex and year of completing training were also determined.

Patients were defined as having been screened for high blood cholesterol if there had been a cholesterol measurement within the past five years. Routine chemistry panels are not available in our institution. Computerized laboratory reports are available in all records. For those that had no documented cholesterol level, hospital computer records were checked to ensure completeness of data collection. In addition, progress notes were reviewed to ascertain whether a patient reported having a cholesterol level checked elsewhere. Medical records were reviewed for evidence of a lipoprotein analysis in patients in whom it was indicated—all patients with an average total cholesterol level of greater than 6.20 mmol per liter (240 mg per dl), patients at high risk for cardiovascular disease with an average total cholesterol level between 5.15 and 6.20 mmol per liter (200 and 240 mg per dl), and all patients taking lipid-lowering medications.*

TABLE 1.—*Patient Factors Associated With Being Screened for Hypercholesterolemia (N = 993)*

Patient Factors	*Patients, No.*	*Patients Screened, %*	P
Age, yr			
≤35	359	77	
>35	634	87	.001
Coronary artery disease risk*			
High	270	86	
Low	701	78	.01
Ethnicity†			
White	416	84	
Nonwhite	553	77	.05
Medications			
≤2	726	77	
≥3	267	86	.01
Sex			
Male	319	76	
Female	674	81	.10
Insurance			
Private or self-pay	499	78	
Other	494	81	>.25

*Data were missing for 22 patients.
†Data were missing for 24 patients.

The proportion of patients screened for high blood cholesterol levels, the proportion of patients who had lipoprotein analysis done in whom it was indicated, and the proportion of patients taking medications for hypercholesterolemia who had a lipoprotein analysis done beforehand were all determined. Univariate and multivariate associations between patient and provider characteristics and screening for high blood cholesterol and for lipoprotein analyses were compared, using χ^2 and Mantel-Haenszel analyses, including tests for homoge-

*The conversion factor to Système International (SI) units for cholesterol levels is 0.2586, but we have rounded the SI values for ease in remembering them.

neity of effect.[6,7]* Statistical significance was set at .05 (two-tailed). The study protocol was submitted to and approved by the Committee on Human Research at the University of California, San Francisco. Confidentiality was maintained by coding the records without names or subject identifiers.

Results

Most of the patients in the study were women, and nearly two thirds were older than 35 years (Table 1). There were slightly more nonwhite than white subjects. Almost three quarters of the patients were at low risk for cardiovascular disease, and a similar proportion took two or fewer medications.

Of the 993 patients for whom complete data were available, 791 (80%) had been screened for hypercholesterolemia within the past five years. Several patient factors including age, cardiovascular risk status, race, and number of medications were associated with screening for high blood cholesterol in univariate analyses (Table 1). For example, among patients at high risk, only 14% were not screened, compared with 22% of those at low risk. In multivariate analysis, however, only age was independently associated with screening. Analysis by decade confirmed that the trend of increased screening with increasing age was linear: ages 18 to 30, 59%; ages 31 to 40, 81%; ages 41 to 50, 86%; ages 51 to 60, 89%; ages 61 to 70, 91% (χ^2 for trend = 54.4; $P < .0001$). Patients' sex and insurance status were not associated with screening. Although there was no difference in screening between older whites and nonwhites, younger nonwhites were significantly less likely to be screened than younger whites ($P < .0001$) (Table 2).

TABLE 2.—*Hypercholesterolemia Screening in White and Nonwhite Patients*

Race by Age, yr	*Patients, No.*	*Patients Screened, %*	P	P*
≤35				
White	166	77		
Nonwhite	181	58	.0001	
>35				.03
White	250	88		
Nonwhite	372	86	>.25	

*Homogeneity of effect was analyzed.

Lipoprotein analysis was indicated in 235 patients and had been done in 140 (60%) of them. Of the 64 patients taking cholesterol-lowering medications, 59 (92%) had lipoprotein analyses done beforehand. Age was independently associated with the performance of lipoprotein analysis. Race, sex, and number of medications were not associated with the appropriate performance of lipoprotein analyses (Table 3).

No provider characteristics were associated with screening. Although faculty physicians screened a slightly greater proportion of patients for high blood cholesterol than did residents (Table 4), this was confounded by patient age. There was no significant difference in screening between primary care residents and categorical internal medicine residents. Provider gender and year of completing training were also not associated with screening.

*Cary Fox assisted in coding and analyzing data.

Discussion

This study from a university-based general internal medicine practice demonstrated a high rate of compliance with screening recommendations for high blood cholesterol—only 20% of patients had not had at least one cholesterol level checked in the past five years. The screening rate in our practice was higher than that found by Richlie and co-workers in a Department of Veterans Affairs hospital. In their population, 84% of the patients were at high risk for cardiovascular disease, yet the overall rate of screening was only 60%.[8] The screening rate in our practice was also higher than that found among pri-

TABLE 3.—*Patient Factors Associated With Performance of Lipoprotein Analyses*

Patient Factors	*Patients, No.*	*Patients Screened, %*	P
Age, yr			
≤35	28	25	
>35	207	64	.0002
Ethnicity*			
White	84	63	
Nonwhite	145	58	.44
Medications			
≤2	127	52	
≥3	108	69	.01
Sex			
Male	97	53	
Female	138	64	.07

*Data missing for 6 patients.

TABLE 4.—*Provider Characteristics Associated With Screening for Hypercholesterolemia*

Characteristics	*Provider, No.*	*Patients, No.*	*Patients Screened, %*	P
Provider sex				
Male	27	367	79	
Female	34	626	80	>.25
Completed training				
1988 or before	48	107	83	
After 1988	13	886	79	.34
Provider type				
Physician	52	757	80	
Nurse practitioner	9	236	79	>.25
Physician type				
Faculty	15	457	82	
Resident	37	300	77	.10
Resident type				
Traditional	25	115	76	
Primary care	12	149	77	>.25

vate physicians in neighboring communities, where the overall screening rate was 53%.[9]

Because routine chemistry panels are not available in our institution, these cholesterol measurements were intentionally ordered, presumably as either a screening procedure or as follow-up of dietary or drug therapy. Although there was a high rate of initial screening overall, many patients were not appropriately classified by lipoprotein fractions; only 47% of patients in whom lipoprotein analysis was indicated had it done.

The only patient characteristic independently associated with an increased incidence of screening was patient age. Persons older than 35 comprised 88% of the sample, and these patients were screened more often than patients aged 35 and younger (see Table 1). This is in accordance with a 1989 report from the Centers for Disease Control that younger persons were less likely to report having their cholesterol checked or knowing their cholesterol level.[10] This may reflect the persistent controversy over screening low-risk persons.[11]

Patients at high risk for cardiovascular disease were no more likely to be screened for hypercholesterolemia than those at low risk. Although cardiovascular risk status and number of medications were associated with cholesterol screening in univariate analyses, both associations were confounded by age. Older persons were more likely to be at high risk for cardiovascular disease and were more likely to be taking three or more medications.

We were somewhat surprised to find that young whites were screened more often than young nonwhites. This is consistent with other reports of the decreased use of preventive services, such as Papanicolaou smears, by minorities.[12] Older nonwhites, however, were screened as often as older whites. We do not know if the whites in our study were more likely to request that their cholesterol levels be measured, perhaps because of socioeconomic status or educational level. Nor do we know if provider attitude about race was a factor. Because this finding was not substantiated in older patients, we suspect that it was not. Physician differences in preventive practices in white and minority patients have been seen, however. In one study, physicians with predominantly African-American and Hispanic patient populations were less likely to recommend screening mammography and influenza vaccinations when compared with physicians caring for predominantly white patients.[13] These differences may be related to differential reasons for seeking health care. Nonwhites' visits to physicians may more likely be for acute conditions that do not lend themselves to preventive interventions. A third possible explanation is that this is a chance finding. Further studies are needed to verify this finding. Race was not associated with the appropriate performance of lipoprotein analyses. The number of patients in whom lipoprotein analyses were indicated, however, was much smaller than those eligible for screening, making these results difficult to interpret.

No provider characteristics were independently associated with screening for hypercholesterolemia. Although the rate of screening among faculty physicians was slightly higher than that among residents, this finding was confounded by patient age. Faculty physicians cared for more patients older than 35. Interestingly, although primary care internal medicine residents spend more time in the outpatient setting—6 months of each of the last 2 years of residency—and might be expected to be more focused on prevention, their screening practices did not differ significantly from those of categorical internal medicine residents.

Our results confirm that clinicians often fail to do lipoprotein analyses when they are indicated. In one previous study, lipoprotein analysis was indicated in 69% of the sample but was done in only 16% of those in whom it was indicated.[8] Clinicians in our study did substantially better, classifying more than half of patients in whom lipoprotein analyses were indicated. Lipoprotein analysis rates were still low, however, especially in patients younger than 35 years. This low rate of lipoprotein analysis may be related to the need for a return visit to obtain a fasting specimen. We do not know whether this is a problem of patient or provider compliance.

There are several limitations to our study. First, the study was done in a university-based general internal medicine practice in which NCEP guidelines have been widely disseminated. The high rate of compliance with screening recommendations in this setting shows that disseminating information and intensive education can be effective.

Patients without primary providers were excluded, and these patients are generally less likely to receive routine preventive care.[14] Hence, the rates of screening for high blood cholesterol in this population might be expected to be lower.

Finally, our study assessed compliance with the recommendations for screening for hypercholesterolemia, but not with those for the management of high blood cholesterol. Our results complement those of a recent study that assessed compliance with NCEP management guidelines in a group-model university-based health maintenance organization.[15] The investigators found that in the year following the index elevated cholesterol level, 67% of patients who had a cholesterol level of greater than 6.20 mmol per liter (240 mg per dl) had received dietary counseling, but only 14% of them were prescribed a cholesterol-lowering medication. Of those taking a cholesterol-lowering medication, 85% had lipoprotein analyses done beforehand. Future studies must address compliance with recommendations for the management of high as well as borderline-high blood cholesterol.

We conclude that although providers in this university-based general internal medicine practice are screening most high-risk patients for hypercholesterolemia, screening rates were lower in younger patients, especially in young nonwhites. Many patients with elevated cholesterol levels are not appropriately classified as to their low-density-lipoprotein status. A high level of compliance in screening for hypercholesterolemia was seen

in this university-based general internal medicine practice. We suggest that studies be done to address whether such high levels of compliance can be achieved in other practice settings and to further assess compliance with recommendations for the management of high blood cholesterol.

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Articles

Trousseau's Syndrome

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We report 4 cases of Trousseau's syndrome, in which spontaneous recurrent or migratory venous thromboses, arterial emboli caused by nonbacterial thrombotic endocarditis, or both, develop in a patient with a recognized or occult malignant tumor. The clinical course of 3 of the patients emphasizes a key point: The occurrence for no known reason of thromboses preventable by anticoagulation therapy with heparin but not with warfarin sodium should alert a physician to focus diagnostic efforts on uncovering an underlying malignant lesion. Thromboses may occur months to years before the tumor is discovered, and a thorough negative initial examination does not obviate the need for a continuing search. Patients with Trousseau's syndrome have persistent low-grade intravascular coagulation, and therapy with heparin should be continued indefinitely. Stopping heparin therapy for even a day may permit a new thrombosis to develop. Immunostaining a biopsy specimen from 1 patient provided evidence that 2 properties of a neoplastic lesion are required for the syndrome to develop: The malignant cells express surface membrane tissue factor, and structural features of the tumor permit the malignant cells or vesicles it sheds to be exposed to circulating blood.

(Callander N, Rapaport SI: Trousseau's syndrome. West J Med 1993 Apr; 158:364-371)

Thrombosis occurs frequently in patients with a malignant tumor as an isolated episode of deep venous thrombosis following surgical treatment or during chemotherapy[1] that responds to standard antithrombotic therapy with heparin and warfarin sodium initially, followed by warfarin alone. A less common but more aggressive thrombotic diathesis is also seen, however, in which a patient with a malignant neoplasm has spontaneous recurrent or migratory episodes of venous thrombosis, arterial emboli due to nonbacterial thrombotic endocarditis, or both. These thrombotic episodes require the continuous administration of heparin and do not respond to the use of warfarin. These findings are designated Trousseau's syndrome, based on Armand Trousseau's observation almost 125 years ago that migratory thrombophlebitis can signal the presence of an underlying visceral carcinoma. In 1977 Sack, Levin, and Bell summarized the essential clinical, pathophysiologic, and therapeutic features of Trousseau's syndrome.[2] More recently, Bell and colleagues described the cases of two patients whose clinical course demonstrated the absolute requirement for heparin therapy in managing Trousseau's syndrome.[3]

Despite its well-described features, however, Trousseau's syndrome may be difficult to recognize and manage in individual patients. We report the clinical findings of four patients whose cases illustrate this difficulty, particularly the fact that recurrent thromboses despite warfarin therapy predict the presence of an underlying malignant tumor. We also offer evidence from one patient and summarize other evidence suggesting that in most patients, the hypercoagulability of Trousseau's syndrome stems from the exposure of tissue factor (thromboplastin) from tumor cells to the circulating blood.

Report of Cases

Case 1

The patient, a 58-year-old woman, had been receiving tamoxifen citrate for a year because of metastatic adenocarcinoma of the breast. A cerebral embolism developed while she was vacationing abroad, and a second cerebral embolism developed several days later while she was flying home. On arriving home she was admitted to the University of California, San Diego (UCSD), Medical Center, where an echocardiographic study revealed no cardiac abnormality. Antithrombotic therapy was started with intravenous heparin and warfarin. After nine days the heparin therapy was stopped, and two days later the patient was discharged with a prothrombin time of 24 seconds and was given instructions to continue taking 5 mg of warfarin daily. On the day of discharge she noticed leg pain while walking but did not mention this.

When next seen 11 days later, she had a swollen, tender left leg, and a venogram revealed a deep venous thrombosis. The prothrombin time was 17 seconds and fibrin degradation products measured as the plasma D-dimer concentration were 2,000 to 4,000 ng per ml (normal <250 ng per ml). She was admitted to hospital, and intravenous heparin therapy was begun. Warfarin therapy was continued at an increased dosage of 8 mg

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
INR = international normalized ratio
MRI = magnetic resonance imaging
UCSD = University of California, San Diego

daily, and tamoxifen therapy was discontinued. The administration of heparin was stopped after ten days, at which time the D-dimer test was negative. She was discharged with the expectation that the combination of a higher dosage of warfarin and the elimination of tamoxifen therapy would eliminate the need for long-term anticoagulation therapy with subcutaneous heparin, which she wished to avoid.

When seen six days later, the patient was asymptomatic. The prothrombin time was 24 seconds (control 12 seconds [INR 6.5*]). A D-dimer test result, however, not available until after the patient had left the clinic, was positive at a concentration of 4,000 to 8,000 ng per ml. She was contacted and returned to the clinic three days later, at which time she had new left leg pain. The prothrombin time was 26 seconds (INR 8.0), the activated partial thromboplastin time 49 seconds (normal <30 seconds), and the plasma D-dimer level 8,000 to 16,000 ng per ml. Venography failed to visualize the venous system of the left leg, and a venacavagram showed occlusion of the inferior vena cava to the level of L-4. The findings of a ventilation-perfusion scan were consistent with a pulmonary embolism.

The patient was admitted to hospital, a Greenfield filter was placed to prevent additional pulmonary emboli from the inferior vena caval thrombus, and intravenous heparin therapy was begun. She improved gradually, and the intravenous heparin therapy was replaced by the administration of subcutaneous heparin, 14,000 U every 12 hours. On this regimen the activated partial thromboplastin time six hours after an injection was about twice the control value and the D-dimer test was negative.

Four courses of combination chemotherapy were given. An attempt to reduce the dose of subcutaneous heparin after the chemotherapy caused the D-dimer level to rise. The patient continued to receive subcutaneous heparin until her death two years later from complications of metastatic disease. She had no other recognized thrombotic events.

Comment. This patient's course illustrates that the use of warfarin cannot prevent a progression or recurrence of venous thrombosis in a patient with Trousseau's syndrome, even when given at a dosage achieving a much higher degree of anticoagulation (prothrombin time 24 to 26 seconds [INR 6.5 to 8.0]) than that currently recommended for managing venous thrombosis in other circumstances (INR 2.0 to 3.0). Measuring fibrin degradation products with the D-dimer test provided an early clue that antithrombotic therapy with warfarin was ineffective.

Case 2

Seven months before being seen at the UCSD Medical Center, a 31-year-old woman's left leg became swollen and tender after she drove from the Midwest to California. A venogram confirmed the presence of a deep venous thrombosis, and she was admitted to hospital. Her physical examination was notable only for the leg findings. Her prothrombin time, activated partial thromboplastin time, and results of a urinalysis and complete blood count, including platelet count, were normal. Heparin was given intravenously, and warfarin therapy was added on the second hospital day. Heparin therapy was stopped on the fifth hospital day. The prothrombin time on the seventh hospital day was 26 seconds, and she was discharged.

She returned to the hospital that evening because of shortness of breath, pleuritic chest pain, and hemoptysis. She was referred to a larger medical facility, where a chest x-ray film showed a wedge-shaped density in the posterior basal segment of the right lower lobe suggestive of a pulmonary infarct. In addition, an ill-defined, rounded density of unknown import was noted in the left mid-lung field. The findings of a ventilation-perfusion scan were consistent with a pulmonary embolism of the right lung. A consultant thought that the pulmonary embolism had resulted from stopping heparin therapy prematurely.

After several days of additional intravenous heparin therapy, warfarin therapy was started again. The patient was discharged on a warfarin dosage of 5 mg daily. A prothrombin time two weeks later was 24 seconds. A second consultant, who saw the patient for evaluation of a possible hypercoagulable state, recommended measuring the antithrombin III level and continuing warfarin therapy for six months at a dosage that kept the prothrombin time at 23 to 25 seconds.

Despite continuing warfarin therapy, about two months later the patient had pain and swelling in the right leg. The prothrombin time was 22.4 seconds, the activated partial thromboplastin time 38 seconds, and the platelet count 199×10^9 per liter (199,000 per μl). A venogram revealed extensive deep venous thrombosis of the right leg with thrombus extending into the iliac vein. The patient was referred to an academic medical center, where treatment with intravenous heparin was started again. A mammogram and a pelvic ultrasound study showed no abnormalities. The results of tests for protein C, protein S, antithrombin III, and anticardiolipin antibody were all reportedly normal. After about two weeks, intravenous heparin therapy was replaced by therapy with subcutaneous heparin in a dosage of 14,000 U every 12 hours. The patient was discharged to continue subcutaneous heparin therapy as an outpatient.

Approximately two months later the patient came to the UCSD Medical Center for evaluation of whether she needed to continue taking heparin. She had no constitu-

*When measuring prothrombin time, the international normalized ratio (INR) is obtained by adjusting the ratio of the patient's prothrombin time in seconds to a control prothrombin time in seconds. This is done using a coefficient that relates how sensitive to the effect of warfarin a particular laboratory's thromboplastin is in comparison to a standard World Health Organization thromboplastin preparation.

tional symptoms. She had never smoked and had not used oral contraceptives. Her only medication was heparin, 14,000 U injected subcutaneously at 6 AM and 6 PM daily. The physical examination was unremarkable, as were a blood count and routine blood chemistry values. The platelet count was 242×10^9 per liter (242,000 per μl). The results of coagulation studies were as follows: prothrombin time, 12.8 seconds (control 12.1); activated partial thromboplastin time, 66.4 seconds (control 27.4); and antithrombin III functional activity, 79%, protein C antigen, 108%, total protein S antigen, 116%, and free protein S antigen, 103% of pooled plasma reference standards. The results of a D-dimer test were negative.

A chest x-ray film showed a small left mid-lung-field nodule that appeared unchanged when compared with the film of six months earlier. Because the clinical course was suggestive of the hypercoagulability of malignancy, a computed tomographic (CT) scan of the chest was obtained without delay. It revealed a left upper lobe nodule with satellite lesions, left hilar adenopathy, and a small left pleural effusion. Subcutaneous heparin therapy was discontinued for 24 hours to permit a CT-guided fine-needle biopsy of the pulmonary lesion. Tests done before the procedure revealed an activated partial thromboplastin time of 24.5 seconds (control 25.2) and a D-dimer level that had risen in the interval to 2,000 to 4,000 ng per ml. Cytologic evaluation of the fine-needle aspirate showed features consistent with a poorly differentiated adenocarcinoma. After an evaluation failed to reveal metastatic disease, the patient underwent a left thoracotomy. Although the primary nodule was only 1 cm in size, a frozen section of a hilar node revealed adenocarcinoma, and multiple tiny tumor nodules were present in the lung parenchyma and on the parietal pleura and diaphragm. Because curative resection was not possible, several nodules of tumor were removed, and the incision was closed. Permanent sections confirmed the diagnosis of a poorly differentiated adenocarcinoma of the lung and showed tumor cells within the lumen of the arterioles (Figure 1).

Despite combination chemotherapy, the patient's condition steadily worsened. Because of a modest thrombocytopenia attributed to a fourth cycle of chemotherapy, the heparin dosage was reduced to 12,000 U twice a day. A few days after the dosage reduction, fever and left groin pain developed. An activated partial thromboplastin time six hours after the morning dose of subcutaneous heparin was 31.5 seconds (control 27.8). The fibrinogen concentration was 6.6 grams per liter, and the results of a D-dimer test were positive at 2,000 to 4,000 ng per ml. A duplex ultrasonogram of the left groin revealed a new thrombus within the left femoral vein. Findings resolved with the institution of intravenous heparin therapy, and after three days subcutaneous heparin therapy was resumed at a dosage of 14,000 U twice a day. About two weeks later, the patient moved back to the Midwest, where she died five months later of overwhelming metastatic disease.

Comment. This case illustrates that a thorough search for an underlying malignant neoplasm is indicated regardless of a patient's age if venous thrombosis progresses or recurs while the patient is optimally anticoagulated with warfarin. A venous thrombosis due to other causes for hypercoagulability—a hereditary deficiency of protein C, protein S, or antithrombin III or the presence of antiphospholipid antibodies—should respond to treatment with warfarin. The elevated D-dimer level found 24 hours after discontinuing heparin for the biopsy illustrates how rapidly abnormal clotting may begin when heparin therapy is stopped. Reducing the twice-a-day subcutaneous heparin dosage below that needed to keep the activated partial thromboplastin time in a therapeutic range (1½ to 2 times the control 6 hours after an injection) triggered a new thrombotic event.

Case 3

The patient, a 62-year-old woman, was seen for evaluation because of repeated arterial thromboembolic events. Fifteen months earlier she had had an episode of

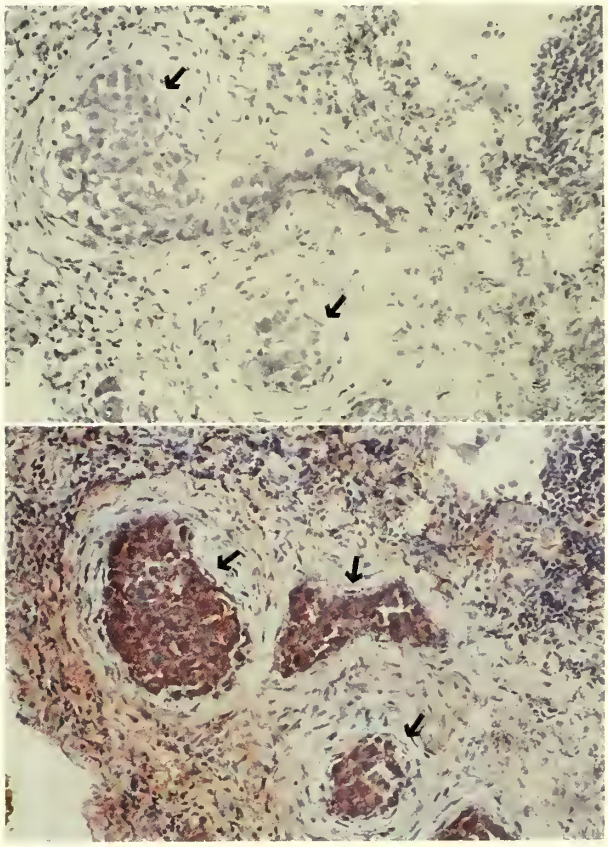

Figure 1.—Top, In this hematoxylin-stained section of a tumor nodule obtained from the patient in case 2, tumor cells **(arrows)** obliterate the lumen of arterioles. The section has been immunostained with a control nonimmune rabbit immunoglobulin (Ig) G and then overlaid with peroxidase-labeled goat antirabbit IgG. The tumor cells display negligible nonspecific staining. **Bottom,** In a contiguous section of the tumor nodule immunostained with rabbit antihuman tissue factor IgG and then overlaid with peroxidase-labeled goat antirabbit IgG, tumor cells **(arrows)** are seen within arterioles. The tumor cells have specifically bound rabbit antihuman tissue factor IgG. In contrast to the cells in the top section, after being overlaid with peroxidase-labeled goat antirabbit IgG, the tumor cells stained an intense purplish brown. Specific staining for tissue factor of tumor cells outside the vessels is also recognizable.

dizziness that was attributed to a transient ischemic attack. A magnetic resonance imaging (MRI) scan done two months later showed a left medial occipitotemporal gyral infarct. A vascular surgeon found normal radial, femoral, and popliteal pulses but absent pedal pulses. Spells of dizziness continued despite treatment with aspirin and dipyridamole, and approximately nine months after the first MRI scan she was admitted to hospital for further study. A blood pressure measurement in the right arm was unobtainable, and the popliteal pulses were no longer palpable. A new MRI scan revealed multiple cerebral infarcts, and cerebral angiography disclosed an occlusion of the left posterior cerebral artery.

Antithrombotic therapy with warfarin was begun. Several weeks later, while the prothrombin time was being kept at twice the control value, evidence of incipient gangrene of the toes of the left foot developed. The patient was again admitted to hospital, and angiography revealed occlusions of both the left and right superficial femoral arteries and also of the right axillary artery. An echocardiogram revealed mild thickening of the mitral valve but no vegetations, intracavitary clots, or masses. A platelet count was 87×10^9 per liter (87,000 per μl). Laboratory tests eliciting normal values included the hemoglobin level, leukocyte count, standard blood chemistry panel, serum protein electrophoresis, antithrombin III level, and measurements of anticardiolipin, anti-DNA, anti-smooth muscle, anti-extractable nuclear antigen, and anti-ribonucleoprotein antibodies.

Warfarin therapy was discontinued and heparin therapy begun. On the ninth hospital day, a left femoral anterior tibial bypass was performed using an umbilical vein graft. This was necessary because venography had shown that the ipsilateral greater saphenous vein was a recanalized postphlebitic system and the right saphenous vein, when removed during an operation for use as the bypass vessel, was found to contain areas of recent and organizing thrombus.

Warfarin therapy was started after the operation, but gangrene of the left leg progressed and several days later the leg had to be amputated below the knee. The graft was patent on pathologic examination, but thrombi were seen in adjacent small vessels.

Warfarin therapy was begun again after the second operation. After ten days, however, necrosis of the toes and heel of the right foot developed, and the right leg was amputated below the knee. Despite continuing warfarin administration at a dosage that kept the prothrombin time in the 26-second range, gangrene of the stump developed. Warfarin therapy was stopped, the stump was revised to an above-the-knee amputation, and the patient was transferred to the UCSD Medical Center.

The physical examination revealed normal fundi, brisk carotid pulses without bruits, and normal cardiac and abdominal findings. The right forearm and hand were dusky red, and the right radial and ulnar pulses were barely palpable. Dressings were present on both stumps. The prothrombin time was 13.9 seconds, the activated partial thromboplastin time 30.3 seconds, and the platelet count 76×10^9 per liter (76,000 per μl). The plasma D-dimer concentration was 8,000 to 16,000 ng per ml. The fibrinogen concentration was 2.67 grams per liter; von Willebrand antigen, 240%; factor VIII activity, 100%; and factor V activity, 88%. Values for factor VII activity, specific prothrombin activity, protein C antigen, and total protein S antigen were all within normal limits, as were tests for antithrombin III and α_2-antiplasmin activity. A test for heparin-induced platelet aggregation was negative.

Because Trousseau's syndrome was suspected, therapy with intravenous heparin was begun at 1,000 U per hour. Within 24 hours the platelet count rose to 165×10^9 per liter (165,000 per μl) and the D-dimer level fell to less than 250 ng per ml. The findings of an admission chest x-ray film and a chest x-ray film taken six months earlier were suggestive of left hilar prominence. A CT scan of the chest showed left hilar and mediastinal adenopathy, and a CT-guided biopsy revealed adenocarcinoma with evidence of psammoma bodies. Mammography, abdominal and pelvic CT scans, thyroid scan, and ultrasonography were normal, and tests for CA 125 and carcinoembryonic antigen were negative. Because a primary tumor likely to respond to treatment could not be identified and the patient's condition was poor, chemotherapy was not attempted. Anticoagulation with subcutaneous heparin was continued at an intermediate-care facility, where the patient died about a month later reportedly of complications of metastatic disease.

Comment. This patient had several arterial occlusive events, presumably embolic from a nonbacterial thrombotic endocarditis, for 15 months before an adenocarcinoma involving hilar and mediastinal lymph nodes was recognized. Evidence of venous thrombosis in both legs was also found. Antithrombotic therapy with warfarin repeatedly failed to prevent new arterial occlusive events, whereas laboratory evidence of intravascular coagulation disappeared within 24 hours of beginning therapy with intravenous heparin.

Case 4

The patient, a 60-year-old man who had received mantle irradiation for stage 2A Hodgkin's disease 19 years earlier, was referred for consultative evaluation of a thrombotic diathesis. The thrombotic disorder had begun almost two years before the consultation with an episode of superficial thrombophlebitis. Shortly thereafter, calf pain developed, and findings of a venogram were suggestive of a deep venous thrombosis. Chest, abdominal, and pelvic CT scans showed no abnormalities except for evidence of a hemangioma of the right lobe of the liver. This had first been seen on a CT scan performed three years earlier as part of a periodic evaluation of the status of the treated Hodgkin's disease.

The patient was given warfarin for three months. A week after therapy was stopped, he again had calf pain and evidence on examination of superficial thrombophlebitis. He was admitted to a hospital for further studies to rule out underlying neoplastic or rheumatologic disease.

The results of a routine chemistry panel, a test for antinuclear antibody, and a test for rheumatoid factor were normal, as was the sedimentation rate. Again CT scans of the chest and abdomen and an abdominal ultrasonogram, bone scan, barium enema, upper gastrointestinal series, and results of bilateral iliac crest marrow biopsies were all essentially normal, revealing only the known hepatic hemangioma.

The patient was treated initially with heparin, which was then replaced with warfarin at a dosage of 10 mg daily. A regimen of prednisone was started because of the possibility of an atypical rheumatologic illness. Three days after being discharged from the hospital on this regimen, superficial phlebitis developed in his right arm, with violaceous discoloration of the dorsum of one foot and bilateral ankle edema.

This development prompted his referral for evaluation to an academic medical center, where he was found to have bilateral carotid bruits, an absent left brachial pulse, and laboratory evidence of intravascular coagulation in the form of a positive plasma protamine paracoagulation test and elevated levels of fibrin-split products. Levels of protein C and antithrombin III were normal, and a test for a lupus anticoagulant was reported as "indeterminant." Embolization of the hepatic angioma was attempted in the hope that this would stop the underlying, low-grade disseminated intravascular coagulation. Two days later the patient was discharged on low-dose subcutaneous heparin therapy, 5,000 U every 12 hours, with the recommendation that it be continued until the disseminated intravascular coagulation resolved.

The following afternoon, acute right upper quadrant pain and tenderness developed. He was admitted to hospital, where he was found to have an activated partial thromboplastin time of 28 seconds (control 26) and a normal platelet count. A laparotomy was done, and a gangrenous gallbladder was removed. Its relation to the attempted embolization was unclear because the cystic artery was found during the operation to be pulsatile. Two days after the operation, twice-a-day administrations of 5,000 U of heparin were resumed. The next morning, however, the patient collapsed while returning to bed from a shower. A ventilation-perfusion scan revealed multiple pulmonary emboli. Heparin was given intravenously in a dosage that was gradually increased to 2,250 U per hour to achieve an activated partial thromboplastin time of twice the control value. He appeared to improve, but four days later bleeding from the gastrointestinal tract began. Heparin therapy was stopped, and he was taken by airplane to an academic medical center for possible placement of an umbrella in the distal inferior vena cava.

Endoscopy revealed two small gastric ulcers. An intravenous drip of heparin at 2,200 U per hour was resumed, and antacids and a histamine-2 blocker were given. Therapy with warfarin was also started. After seven days the heparin therapy was stopped, and two days later the patient was discharged with instructions to continue taking warfarin at a dosage of 7.5 mg daily. The same day, shortly after the patient arrived home, chest pain developed. He was admitted to his community hospital where the findings of a ventilation-perfusion scan were consistent with new pulmonary emboli. Warfarin therapy was stopped and replaced with the subcutaneous administration of 16,000 U of heparin every eight hours.

Over the next six months he continued to receive subcutaneous heparin therapy in a decreasing dosage. He then had another episode of thrombophlebitis. An activated partial thromboplastin time was 41 seconds (control 25), and the heparin dosage was increased to 16,000 U every 12 hours. A month later, another attempt was made to replace heparin with warfarin, but it was abandoned when a test for fibrin-split products disclosed that their level had risen.

Shortly thereafter he was again admitted to hospital, this time for chest and left flank pain thought due to bleeding from overcoagulation with heparin. Another chest x-ray film and abdominal and pelvic CT scans failed to disclose a cause for the pain. After this hospital admission, the heparin dosage was reduced to 6,500 U every 12 hours, and the patient was referred for outpatient consultation to a second academic medical center. A series of coagulation tests, done on plasma from which heparin had been removed by column chromatography, yielded results that were within normal limits, as did a test for anticardiolipin antibodies. Because an autoimmune disorder was suspected, the patient was placed on a regimen of prednisone, 40 mg daily; warfarin therapy was started again, and heparin therapy was stopped after a seven- to ten-day overlap with warfarin. When the heparin therapy was stopped, the patient noted the onset of a burning, prickly, hot feeling in the soles of his feet and shin pain, symptoms he had experienced previously soon after heparin therapy had been stopped. The fibrinogen level fell to 1.69 grams per liter, the platelet count to 39×10^9 per liter (39,000 per μl), and the level of fibrin-split products rose. When heparin therapy was started again, the platelet count and fibrinogen level rose. The patient continued to receive subcutaneous heparin, 16,000 U twice a day, for the next five months.

The patient was then referred to the UCSD Medical Center for consultative evaluation. In addition to the findings cited earlier, the patient had had hypothyroidism and right vocal cord paralysis (with no abnormalities found on bronchoscopy and mediastinoscopy) of several years' duration, which was attributed to complications of radiation therapy for Hodgkin's disease. The physical examination revealed notable wasting of the trapezius and sternocleidomastoid muscles bilaterally, also attributable to the earlier irradiation. A series of coagulation tests was carried out on plasma from which heparin was removed by Ecteola cellulose column chromatography. Results of the following tests were within normal limits: protein C antigen and activity, total and free protein S antigen, antithrombin III antigen and activity, D-dimer test, plasminogen activity, α_2-antiplasmin activity, and euglobulin lysis time. An assay for plasma activity of tissue factor pathway inhibitor (formerly referred to as either extrinsic

pathway inhibitor or lipoprotein-associated coagulation inhibitor) was also within normal limits. In addition, monocytes were isolated from a random specimen of heparinized blood by gradient density separation, and their coagulant activity was measured in a specific assay for tissue factor activity. The patient's monocytes had less measurable tissue factor activity than that found in monocytes obtained from a normal subject.

Thus, no abnormality of a hemostatic factor could be identified that would account for the patient's hypercoagulability. It was recommended that heparin continue to be administered subcutaneously without further attempts to replace heparin with warfarin. Despite the long duration of the hypercoagulable state and earlier extensive examinations failing to reveal an underlying malignant neoplasm, it was also recommended that the patient continue to be evaluated for the possibility of an occult tumor.

The patient's primary physician reported two months later that the patient had had a transient ischemic attack three hours after the second of two 16,000-U doses of subcutaneous heparin were omitted to administer steroids interarticularly for shoulder pain due to osteoarthritis. Nine months after the patient's visit to this institution, that is, almost three years after the first thrombotic episode, it was learned that a right upper lobe infiltrate had been found on a chest x-ray film taken because a cough had developed. A bronchoscopic biopsy specimen revealed an adenocarcinoma. Further evaluation disclosed metastases to bone. Despite the administration of combination chemotherapy, the patient died of complications of metastatic disease about six months later.

Comment. In this patient a continuous hypercoagulable state causing chronic low-grade intravascular coagulation and repeated thrombotic episodes preceded by almost three years the recognition of an adenocarcinoma of the lung. Thrombosis was preventable by full anticoagulation with heparin but not by anticoagulation with warfarin. New manifestations of intravascular coagulation were recognized within hours to days after discontinuing heparin or reducing its dose. The course of the patient's disease shows that thorough, early negative evaluations for a malignant lesion in a patient with continuing thrombotic episodes requiring heparin for control do not obviate the need to search for underlying malignancy.

Discussion

Trousseau's syndrome, defined as spontaneous recurrent or migratory episodes of venous thrombosis, arterial emboli due to nonbacterial thrombotic endocarditis, or both, occurring in a patient with an underlying malignant neoplasm, is readily recognized when the patient has an established diagnosis of malignant tumor. In contrast, as documented repeatedly in the literature[2-6] and illustrated by the courses of three of the four patients described here, recognition may be delayed and difficult when thrombotic episodes begin before the malignant lesion is discovered.

The courses of our patients' disease highlight three key diagnostic points:

- If a patient begins to experience venous thromboses or arterial emboli preventable by anticoagulation with heparin but resistant to anticoagulation with warfarin, then the patient should be assumed to have an underlying malignant tumor. Primary diagnostic efforts should focus on finding the tumor.
- A small tumor may be difficult to find. In the absence of definitive evidence, even minimal or questionable findings mentioned on reports of imaging procedures require further investigation. Because the lung is a frequent, if not the most common, primary site for tumors producing Trousseau's syndrome,[2,3,6-11] possible abnormalities seen on radiographic examination of the chest deserve particular attention.
- The fact that thromboses occur over a period of months to years without a tumor becoming manifest is not assurance against a tumor being present.[2-6,9] As our fourth case illustrates, repeatedly negative thorough examinations for malignancy in the early months of a patient's illness do not obviate the need for continuing the search.

Several features of the management of Trousseau's syndrome deserve comment. Thrombotic episodes may cease in a rare patient in whom a localized tumor can be resected,[4] and the syndrome may subside temporarily in a patient with a good response to chemotherapy or radiation therapy. Antitumor therapy, however, seldom induces complete remissions in the types of tumors associated with Trousseau's syndrome.[2,5-11] Once the diagnosis of Trousseau's syndrome is made, most patients must continue to receive heparin therapy for the rest of their lives to prevent new thrombotic events. This can usually, but not always,[3] be accomplished by giving the heparin subcutaneously in a full therapeutic dose. Stopping heparin therapy for only a few hours can reactivate clotting[2,3] and, as happened in the fourth case reported here, can precipitate a thrombotic event. In patients in whom a surgical procedure may be needed for diagnosis of the underlying neoplastic disease, heparin therapy should be continued until just before the operation and begun again after the operation as soon as active bleeding has subsided.

Monitoring levels of fibrin degradation products with the D-dimer test may prove helpful in adjusting the heparin dose. New thrombotic events will inevitably follow attempts to replace heparin with warfarin, even when warfarin is given in doses that prolong the prothrombin time substantially beyond recommended therapeutic ranges.

An analysis of clinical, pathologic, and experimental data provides an understanding of the pathogenesis of Trousseau's syndrome. The rapidity with which a new thrombotic event may occur when heparin therapy is stopped represents strong indirect evidence that the blood is being exposed *continuously* to an agent or agents capable of initiating the coagulation process. Laboratory test

results indicative of chronic, low-grade, disseminated intravascular coagulation[2,3,12] provide direct evidence for this conclusion.

Cytokine-induced expression of procoagulant activity on macrophages or other host cells has been postulated as a cause for the deposition of fibrin around tumor cells in tissues.[11,13] This mechanism seems an unlikely explanation for intravascular coagulation in patients with Trousseau's syndrome. It cannot account for why Trousseau's syndrome develops in a patient with a small, occult tumor whereas in most patients with a malignant tumor, including those with extensive disease, it does not. Moreover, there is little convincing direct evidence that tumors associated with Trousseau's syndrome induce hypercoagulability in circulating mononuclear cells. For example, a sonicate prepared from mononuclear cells freshly isolated from the peripheral blood of our fourth patient possessed less measurable tissue factor activity than did a sonicate prepared from control mononuclear cells. In a study in which the recalcification time of citrated whole blood incubated for two hours at 37°C was taken as a measure of the tissue factor activity of circulating monocytes, individual values obtained from normal controls and from patients with solid tumors overlapped considerably.[14] The mean level of tissue factor activity of unstimulated mononuclear cells from patients with lung cancer after culture and sonication differed only minimally from the mean obtained from normal subjects.[15]

Therefore, hypercoagulable material from the tumor itself, rather than an indirect effect of the tumor on host cells, seems a likely cause for the essentially continuous, low-grade, intravascular coagulation present in patients with Trousseau's syndrome. As our fourth case illustrates, the tumor may be small enough to escape detection for months to years. Thus, a structural or biochemical property of a neoplastic lesion that permits a continuing exposure of the blood to tumor cells, vesicles shed from their membrane,[16] or other tumor products, rather than tumor size, would appear to be an essential component of the pathogenesis.

Evidence for this has long existed. Tumor present within blood vessels has been described in patients with Trousseau's syndrome due to pancreatic carcinoma,[17,18] in a patient with colon cancer and disseminated thrombosis,[19] and in patients with metastatic cancer, hypofibrinogenemia, and a resultant acute hemorrhagic syndrome.[20] Histologic sections of the surgical biopsy in the second patient reported here provide an example of tumor cells growing within the lumens of blood vessels in a patient with Trousseau's syndrome.

What tumor procoagulant material triggers the intravascular coagulation? In 1938 Sproul described the association of multiple thromboses with carcinoma of the body or tail of the pancreas and noted that many of the tumors were mucin-secreting carcinomas.[21] Subsequent pathologic reports also suggested a relation between mucus-producing carcinomas and thrombotic events.[17,22,23] Moreover, partially purified mucin was reported to contain a procoagulant activity that accelerated the consumption of fibrinogen when infused into rabbits; this differed from tissue factor in that it activated factor X in the absence of factor VII.[24] It was postulated that mucus entering the circulatory system could explain the frequency of coagulation disorders in patients with mucin-producing adenocarcinoma.

In an extensive study of the pathologic characteristics of pancreatic carcinoma, an association could not be confirmed between the ability of the carcinoma to produce mucin and the presence of multiple thrombi.[25] No association with mucin secretion could be established in a pathologic study of malignant tumors causing nonbacterial thrombotic endocarditis.[10] In individual patients with Trousseau's syndrome[3] and in the biopsy specimen obtained from the second patient reported here (see Figure 1), mucin is not a feature of the pathologic description of the tumor. In an experiment performed in the UCSD Medical Center laboratory, an extract of mucin obtained from an ovarian cystadenocarcinoma was found to catalyze the activation of factor IX and factor X (D. T. Le, PhD, MD, N. Callander, MD, L. V. M. Rao, PhD, unpublished data, January 1991). The activity in the mucin appeared to be tissue factor, because adding either anti-tissue factor IgG or anti-factor VII IgG to the extract blocked its ability to activate factors IX and X. Thus, data from both pathologic and functional studies fail to support the hypothesis that a procoagulant material unique to mucus triggers intravascular clotting in patients with Trousseau's syndrome.

A cysteine proteinase called cancer procoagulant, which can activate factor X directly, has been isolated from malignant tissue and characterized.[26] Whether this material contributes to the systemic hypercoagulability of some patients with Trousseau's syndrome is unknown. Evidence could not be obtained, however, that cancer procoagulant contributed to the coagulant activity of extracts of gastric and colorectal cancer tissue,[27] two types of tumors associated with Trousseau's syndrome. Moreover, a specimen of cancer procoagulant provided by Stuart G. Gordon, MD, had only weak activity as a factor X activator compared with the activity of factor VIIa-tissue factor complexes or Russell's viper venom (L. V. M. Rao, PhD, and S. I. Rapaport, MD, unpublished data, June 1984).

In contrast, considerable evidence supports the hypothesis that the exposure of the blood to tumor cell tissue factor produces the systemic hypercoagulability of Trousseau's syndrome. Procoagulant activity with the properties of tissue factor has been identified in gastric, colorectal, and renal cancer tissue.[27,28] Tissue factor antigen has been demonstrated by immunostaining in small cell carcinoma of the lung[29] and in colon cancer.[30] Moreover, in a recent study in which a variety of tumors were immunostained for tissue factor apoprotein, histologic sections from tumors commonly associated with the Trousseau's syndrome—lung (including bronchoalveolar cell carcinoma, small-cell carcinoma, and large-cell adenocarcinoma), pancreas, colon, gastric, and breast—frequently stained intensely for surface membrane tissue

factor apoprotein.[31] Finally, tumor cells staining brightly for tissue factor apoprotein were strikingly demonstrated within small blood vessels in the biopsy of the second case reported here (Figure 1-B). Surely in this patient we need not postulate the entrance into the circulation of a material other than tissue factor to account for a continuing, low-grade intravascular coagulation leading to recurrent thrombosis.

A continuing exposure of blood to tissue factor in patients with Trousseau's syndrome might also explain why anticoagulation with heparin but not with warfarin prevents thromboses. Recent evidence indicates that heparin can potentiate in plasma the anticoagulant effect of tissue factor pathway inhibitor, the Kunitz-type inhibitor formerly referred to as extrinsic pathway inhibitor, or lipoprotein-associated coagulation inhibitor.[32,33] It is now thought that this inhibitor serves as an essential natural anticoagulant helping to protect humans from possible thrombotic complications arising from intravascular tissue factor-dependent coagulation.[34] Further studies of the ability of heparin specifically to inhibit tissue factor-dependent blood coagulation seem worthy of pursuit.

We conclude that in most patients, although possibly not every patient, two properties of a tumor can account for the pathogenesis of Trousseau's syndrome: The first is that the malignant cell expresses tissue factor on its external surface. The second is that the tumor cells are anatomically positioned so that cells or vesicles shed from them are exposed to the circulating blood, either directly or by their entrance into the circulatory system from the lymphatic system.

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Articles

Chelation Therapy in Workers With Lead Exposure

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Occupational lead overexposure remains a major problem. To evaluate the settings in which physicians appropriately prescribe chelation therapy for lead exposure, 7 cases were identified from physician phone calls and mandatory laboratory reporting of elevated blood lead levels to the California Department of Health Services. In the 2 workers with the highest blood lead levels (both of whom had severe symptoms), treatment was indicated. Physicians inappropriately prescribed chelating agents to workers with ongoing lead exposure as prophylaxis against rising blood lead levels and to treat atherosclerotic heart disease. Workers' personal physicians identified lead overexposure in 5 of the 7 cases. Workplace lead medical surveillance programs mandated by the federal Occupational Safety and Health Administration were inadequate in all 5 of the workplaces where information was available.

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Occupational lead overexposure remains a major problem, especially in California. The California Occupational Health Program, California Department of Health Services (CDHS), received reports of blood lead levels above 1.20 μmol per liter (25 μg per dl) from 4,069 adults in the first three years since a state law mandating laboratory reporting took effect in 1987. Most cases result from occupational exposure.

In 1978 the Occupational Safety and Health Administration (OSHA) promulgated a comprehensive lead standard,[1,2] emphasizing the primary prevention of lead toxicity by the control of exposure in the workplace. The standard requires many lead-using employers to have physician supervision of a medical surveillance program—including periodic blood lead testing and medical evaluations—for the early detection of lead overexposure. For workers with blood lead levels of 2.40 μmol per liter (50 μg per dl) and above, OSHA mandates removing them from lead exposure, retaining their wages and benefits, and requiring them to receive more frequent medical evaluations and blood lead testing. Effects on the hematologic, neurologic, and reproductive systems have been demonstrated in apparently healthy workers with blood lead levels of less than 2.40 μmol per liter.[3]

Because lead toxicity indicates the failure of preventive measures, treatment is a last resort. There is no specific antidote that reverses lead poisoning, but chelating agents such as edetate calcium disodium, dimercaprol (British antilewisite), penicillamine, and, as of this year, succimer are available to enhance the renal excretion of lead. Although most physicians agree that the use of chelating agents is indicated in patients with severe symptomatic lead poisoning (encephalopathy, colic, paresis),[4] recommendations in standard texts and the Poisindex for chelation therapy in adults with mild or no symptoms are divergent.[5-8] This investigation was undertaken to describe and evaluate chelation use in California workers with lead exposure.

Patients and Methods

This report consists of chelation cases that came to the attention of CDHS between July 1989 and January 1991. Chelation cases were defined as patients for whom a physician prescribed chelation therapy. During this period, about 800 persons with blood lead levels greater than 1.93 μmol per liter (40 μg per dl) were reported to CDHS. Among the approximately 90 persons whose blood lead reports of 2.90 μmol per liter (60 μg per dl) or greater were received during the study period, we identified five chelation cases—cases 1, 2, 5, 6, and 7 (Table 1)—through routine follow-up interviews of the physicians. Two more workers—cases 3 and 4—with blood lead levels of 1.93 and 2.70 μmol per liter, respectively, were brought to our attention by physicians seeking technical assistance. Cases were excluded if chelation was prescribed outside of California, for the purpose of diagnosis, or to a patient whose exposure was not occupational.

At the time of the initial interview by CDHS staff, patients were asked if they were removed or transferred from the job held when the blood lead test was taken. At the time chelation therapy was prescribed, any change in work location was considered removal under the lead standard, although it was not possible to determine if lead exposure was substantially diminished in the new work area in the absence of industrial hygiene monitoring data from these work sites.

Symptoms consistent with lead toxicity were ascertained by standardized interviews by CDHS staff who asked patients and physicians about problems related to the nervous, gastrointestinal, musculoskeletal, hemato-

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ABBREVIATIONS USED IN TEXT

CDHS = California Department of Health Services
OSHA = Occupational Safety and Health Administration

logic, and reproductive systems. Confirmation of interviews using medical charts was not carried out. Standardized interviews of employers of workers with blood lead levels of 2.90 μmol per liter and greater included questions on medical surveillance programs in their work sites.

TABLE 1.—*Occupotionol Leod Chelotion Coses Reported to California Deportment of Heolth Services, July 1989 to Jonuory 1991*

Cheloting Agent/ Cose #	Peok Blood Leod Level, μmol/liter (μg/dl)	Transferred From Usuol Job*	Symptoms Consistent With Leod Toxicity	Occupation	Adequote Medicol Surveillonce Program
Oral Penicillomine					
1 . . .	3.18 (66)	No, Yes	Headaches, fatigue	Foundry worker	No
2 . . .	3.23 (67)	No, Yes	No	Radiator repairer	No
Outpotient Edetote Colcium Disodium (IV)					
3 . . .	1.93 (40)	Yes, Yes	No	Radiator repairer	†
4 . . .	2.70 (56)	Yes, Yes	No	Lead burner	†
5 . . .	2.90 (60)	Yes, Yes	No	Radiator repairer	No
6 . . .	4.92 (102)	No, No	Myalgias	Radiator repairer	No
Inpotient Edetote Colcium Disodium (IV) ond Dimercoprol (IM)					
7 . . .	10.62 (220)	Yes, Yes	Encephalopathy, abdominal colic	Ceramics glazer	--

IM = intramuscular, IV = intravenous

*Answers in column refer to being transferred from usual job "at initial contact" and "at time of chelation therapy."
†Information not available.

Results

Seven physicians prescribed chelating agents to seven workers from different workplaces (Table 1). Agents used were oral penicillamine, intramuscular dimercaprol, and edetate calcium disodium administered intravenously on an inpatient or outpatient basis. Three of the patients (1, 6, and 7) had symptoms consistent with lead toxicity. Of these, patients 6 and 7 had the highest blood lead levels and presented to emergency departments with myalgias (patient 6) and abdominal colic with encephalopathy (patient 7).

Most physicians said their goal of treatment was to lower blood lead levels. The physician of patient 4 said that the worker requested chelation treatment so that he would not be rejected for employment at another lead-using company. Physicians said they prescribed chelation agents to patients 3 and 5 to treat atherosclerotic heart disease attributed to chronic lead toxicity. Two of the treated workers (patients 1 and 4) said they had never been informed of the chelating agent's side effects.

In five workplaces, medical surveillance programs mandated by OSHA lead regulations were inadequate in that the employer provided no blood lead testing or provided testing without physician supervision. Three workers (5, 6, 7) with blood lead levels of 2.90 μmol per liter or higher came from work sites with no employer-sponsored blood lead testing. Workers' physicians ordered the blood lead test for these and in cases 3 and 4. Employers of patients 1 and 2 reported that they order blood lead tests from laboratories and receive and interpret the results without physician involvement.

At the time of the initial patient interview by CDHS staff, patients 1, 2, and 6 reported they had not been removed from the job they had when the blood lead test was obtained. Once physicians prescribed chelation agents, they were able to ensure removal from lead exposure for all but patient 6, who was self-employed and did not comply with the physician's recommendation.

Discussion

This investigation identified several types of chelation therapy misuses: in the setting of ongoing exposure, as prophylaxis against rising blood lead levels, and to treat atherosclerotic heart disease. By contrast, chelation therapy was clearly indicated for the two workers with the highest blood lead levels who presented to emergency departments with symptoms consistent with lead toxicity. The practice of the use of chelation agents in asymptomatic or mildly symptomatic workers was also identified.

Chelation therapy prescribed in patients with ongoing lead exposure (case 6) is not appropriate medical practice.[9,10] The removal from lead exposure is the initial treatment of choice for workers with elevated blood lead levels and is required by OSHA for workers with blood lead levels at or above 2.40 μmol per liter. In a group of smelter workers, chelation therapy without removing the workers from lead exposure failed to prevent adverse lead-induced effects.[11] In addition, chelation therapy confuses the management of workers with lead exposure because it is difficult to then use the blood lead level to assess current exposure, a principal use of blood lead analysis.

The routine use of chelating agents to prevent rises in blood lead levels (case 4) or the development of symptoms is considered "prophylactic chelation" by OSHA, which prohibits such practice by any person retained or supervised by lead-using employers,[1,2] and constitutes inappropriate medical practice. Because physicians employed or contracted by an employer are not shielded by workers' compensation law, they can be held liable for medical malpractice for the inappropriate care of workers.

This investigation revealed the use of chelation agents to treat atherosclerotic heart disease (cases 3 and 5). Evidence that chelation therapy with edetate calcium disodium is ineffective in treating atherosclerosis led the California Medical Board to consider this practice unacceptable.[12,13]

This investigation also found physicians prescribing chelation agents for asymptomatic workers (patients 2 through 5) and a worker with mild symptoms (patient 1). Theoretic benefits of chelation therapy in these settings include preventing organ deposition (if exposure is acute), preventing or reversing end-organ damage, and increasing the long-term rate of lead excretion to decrease the total body lead burden. Unfortunately, the first two potential benefits have not been proved, and Hryhorczuk and co-workers have presented data that raise questions about the last.[14] They found no significant association between the overall blood lead elimination half-time and the total amount of edetate calcium disodium received. They comment that the failure of chelation therapy to increase the long-term rate of lead excretion is probably due to the fact that each chelation course removes only a small fraction of the total body burden.

Both edetate calcium disodium and penicillamine can have substantial adverse effects, including renal damage and interference with trace mineral metabolism. Penicillamine therapy has also been associated with adverse hematologic effects. A study in animals raised worrisome questions about the redistribution of lead from the blood to the soft tissues, including the central nervous system, due to edetate calcium disodium therapy.[15,16] Dimercaprol can cause hypertension and gastrointestinal and nervous system symptoms.[8] Weighing the lack of proven benefit against the risk of chelation-induced adverse effects, some physicians have maintained that workers with elevated blood lead levels and no symptoms or symptoms of early mild lead toxicity are best managed by removing them from lead exposure and closely observing them.[5]

Succimer use, by contrast, produces a short-term reduction in brain and kidney lead levels in animals and appears to induce only a small increase in renal zinc and copper excretion, without other notable adverse reactions, based on limited experience to date.[6] These possible advantages may prompt clinicians to treat asymptomatic or minimally symptomatic adults, for whom the disadvantages of previously available chelators dissuaded such treatment.[17] In the workplace, however, "the step from this practice [chelating asymptomatic workers] to the prophylactic use of these agents is a small one."[18(p564)] Chelation initially lowers blood lead levels and therefore may decrease the length of time an employee must be away from lead exposure and provided medical removal protection benefits under the OSHA standard. Employers may thus be encouraged to rely on chelation rather than instituting controls to prevent lead exposure.

This investigation documented the practice of employers ordering blood lead testing directly from clinical laboratories and interpreting the results themselves, without the physician supervision mandated by OSHA. California law specifically requires that laboratory tests be ordered by and reported only to licensed health professionals.[19] Laboratories violating this provision are subject to having their licenses suspended or revoked.

This investigation has several limitations. Given the incomplete collection of cases of occupational lead overexposure, these cases may not accurately describe the extent and circumstances of chelation use in workers. Only two of the seven patients had their blood lead tests provided by the employer, a finding consistent with the estimate that only 3% of the 230,000 California workers with possible exposure to lead have routine blood lead testing at work.[20] Another CDHS study found that 35% of workers overexposed to lead reported going to a private physician to obtain blood lead testing (California Occupational Health Program, "Profile of California Adult Index Cases With Elevated Blood Lead, 1988-1989," unpublished report, February 1990). This investigation's finding that personal physicians—not employer-contracted physicians—ordered the blood lead tests and thus detected lead overexposure in five of the seven cases highlights the key role of primary care physicians.

Even among workers whose blood lead levels were reported to CDHS, this investigation could not uncover all cases of chelation use. Because of limited resources, only physicians receiving reports of blood lead levels of 2.90 μmol per liter or higher are systematically questioned about chelation use. (At the time of their interview by CDHS staff, two other physicians considered prescribing oral penicillamine for four workers but were dissuaded from doing so after consultation with CDHS or other occupational medicine physicians.)

This study did not address the use of nonprescription agents purported to lower blood lead levels. The CDHS has received reports from lead casting workers and workers at indoor shooting ranges of employer policies encouraging the use of vitamins and milk in the absence of comprehensive medical surveillance programs. The peak blood lead levels of 3.28 and 4.39 μmol per liter (68 and 91 μg per dl) in these workplaces suggest that these policies were ineffective in controlling lead exposure.

Recommendations

Clear and consistent guidelines addressing the diagnostic workup and chelation use in workers with exposure to lead are needed. Physicians considering chelation therapy are strongly urged to consult with colleagues who are experienced in handling such cases and who are up-to-date on the toxicologic literature, including newer agents. University occupational medicine departments or poison control centers are two sources of knowledgeable clinicians.

Treatment using chelation agents represents the failure to prevent lead overexposure and should trigger further follow-up. Physicians caring for workers with elevated blood lead levels can play a key role in identifying others at risk and in prompting actions by workers, employers, and governmental agencies to control lead exposure in workplaces. A physician-supervised medical surveillance program is critical for the early detection of

lead overexposure before symptoms or end-organ damage occurs in the index cases, their co-workers, or their family or community that may be at risk from take-home exposures or off-site migration.

Note: The Occupational Lead Poisoning Prevention Program, CDHS, has developed educational materials about lead and provides consultation for health care professionals, employers, and employees. For more information, call (510) 540-3448 or write to the Occupational Health Surveillance and Evaluation Program, CDHS.

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Articles

Brief Psychotherapy in Medical Practice
Keys to Success

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For physicians faced with helping their patients cope with difficult medical problems, solution-oriented psychotherapeutic techniques provide brief, effective interventions. These approaches offer "skeleton keys" that can be used in a broad patient population. They include clarifying the meaning of the medical illness, therapeutic reframing, projection of the problem, role reversal, and face-saving techniques.

(Eisendrath SJ: Brief psychotherapy in medical practice—Keys to success. West J Med 1993 Apr; 158:376-378)

When patients have trouble coping with medical problems, physicians may give psychotherapeutic help without referring to a psychiatrist or other mental health professional. New concepts based on solution-oriented theories coupled with brief psychotherapeutic techniques offer primary care physicians effective ways to help their patients.

In solution-oriented psychotherapy, certain interventions are viewed as skeleton keys that work with a variety of patients.[1,2] These "solutions" do not require in-depth psychiatric assessments, but they do require a positive relationship between patient and physician and empathy for the patient's perspective. They differ from psychoanalytically derived techniques that require an understanding of a patient's psychological history and development.[3,4] Psychoanalytic approaches are often time-consuming, and most physicians have not been trained in those techniques. In contrast, physicians learn solution-oriented approaches rapidly and can often apply them in one meeting, relying primarily on knowledge of the patient's current emotional state. Several of these techniques will be examined in detail.

Clarifying the Meaning of Illness

Defining the unique meaning of a disease for a patient often leads to decreased distress. Learning who else the patient knows who had the disease, where in the life cycle the illness is occurring, or what fears the patient has about the illness are crucial to understanding its meaning.[5] Clarifying the meaning allows the patient to feel genuinely understood, and the physician may be able to intervene directly.

Case Example 1

The patient, a 78-year-old man, was admitted to the vascular surgery service for a below-the-knee amputation necessitated by peripheral vascular disease. Despite an excellent physical recovery after the operation, the patient appeared severely depressed. The physician assumed the patient was concerned about his newly limited mobility and his changed body image. Discussions of these issues did not lessen the patient's depressive symptoms. The physician then asked the patient what worried him most about the amputation. The patient replied that he was most concerned about being able to fulfill his "conjugal duties." Once this issue was clarified, the physician met with the patient and his wife to discuss this concern openly. In the course of this meeting, the patient's wife offered to try various sexual positions to compensate for difficulties caused by the amputation. The physician was thus able to focus the discussion on the likelihood of the couple's having intercourse successfully, and the patient responded by becoming less depressed and more hopeful about his future.

Reframing

Reframing is a powerful technique that allows a person to change the meaning of a situation by seeing it from a previously unconsidered viewpoint.[6] When physicians use reframing with medically ill patients, they must first understand how patients see their problems. The physician may then use suggestion and persuasion to present patients with a different perspective.

Case Example 2

The patient, a 53-year-old construction foreman, was admitted to the coronary care unit (CCU) with a myocardial infarction. When informed of his diagnosis, he became less compliant with his medical care, getting out of his hospital bed to demonstrate that he could do just as many pushups as he could before entering the hospital. He even raised the idea of signing out of the hospital against medical advice. On speaking with the patient and his family, the attending physician learned that the man was an amateur weightlifter who took considerable pride in his physical strength. He perceived the myocardial infarction and the necessary stay in the CCU as a threat to his masculinity. The physician then reframed the situa-

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tion for the patient by saying, "It takes a strong man to put up with what we are asking of you," recasting the passivity of bed rest as a task that required a great deal of strength. The patient accepted this view of his situation and complied with the rest of his treatment in the CCU.

Case Example 3

The patient, a 32-year-old man with ulcerative colitis, underwent a colectomy after ten years of medical treatment. After the operation the patient became depressed about having a permanent, disfiguring ileostomy, so his surgeon requested a psychiatric consultation. In reviewing the patient's history with him, the psychiatrist noted that the patient had suffered fatigue, frequent hospital admissions, and the need to plan his day around the location of bathrooms. The psychiatrist suggested that the patient might see his ileostomy as contributing to an improvement in his health and life-style, not just as a loss of his bodily integrity. His preoperative symptoms were all expected to resolve, and he no longer had a serious risk of cancer. This alternative view helped the patient resolve his depression.

Although reframing could be considered a form of manipulation, it is manipulation that serves the patients, not the physicians. Reframing a frightening medical situation or procedure so a patient can tolerate it more easily is clearly in the patient's best interest.

Projection of the Problem and Role Reversal

Many patients have difficulty viewing their own situation with objectivity or with the compassion they give to others. Projection is a specialized form of reframing that allows patients to view their problem differently by encouraging them to project it onto someone else. For some patients, asking them to project their situation onto a spouse—in essence, imagining a role reversal—can be especially useful in clarifying their views. But as case 7 in this section demonstrates, there are times when this technique is ineffective.

Case Example 4

The patient, a 59-year-old male executive, had severe coronary artery disease and underwent a coronary artery bypass graft after an episode of substantial arrhythmia. One month after discharge, his cardiologist referred him for psychiatric consultation for persistent postoperative depression. The consultant found that the patient believed his feeling fearful about his medical condition and his operation was evidence of "weakness." He thought he should have been able to handle his distress in a more manly way. The consultant asked what he would think of a friend who was similarly distressed. In particular, the consultant asked whether the friend would have seemed less manly. The patient replied that his hypothetical friend's response would have appeared reasonable and perhaps even a sign of strength in that he expressed his feelings so openly. The consultation concluded with the patient being more accepting of his feelings about his own frightening medical experience.

Case Example 5

The patient, a 42-year-old woman, was undergoing a bone marrow transplant for leukemia. During her chemotherapy she began to talk about terminating her treatment. Her oncologist found that she was depressed because she sensed that she was a burden to her husband and children, despite the potential for cure after her bone marrow transplant. The oncologist asked her how she would feel about the situation if her husband were the one with leukemia. Would she want him to undergo the treatment, or would she feel that it would be too much of a burden? She immediately replied that she would want him to undergo the treatment, and she could see that he felt the same way about her. Her depression and desire to terminate her treatment resolved after this discussion.

Case Example 6

The patient, a 39-year-old woman, underwent a mastectomy for breast cancer. After her operation she told her surgeon she was depressed and concerned about her husband's reaction to the change in her body. When asked how she would feel if her husband had an amputation of a limb, she replied that she would still love him. The surgeon suggested that the husband might have a similar response to her operation. This reassured her, but she was still uncertain about her husband's response, so the surgeon suggested that she ask him about his feelings. Her husband told her that she was more than "a breast" to him and that he was happy simply to have her alive. Her depression cleared.

Case Example 7

A 30-year-old Sikh Indian man underwent an emergency colectomy and had an ileostomy. Depressed postoperatively, he said he thought he would no longer be acceptable to his wife who was in Europe at the time. When asked if he would reject his wife if she had undergone a similar operation, he replied he would definitely reject her because his religion prohibited handling of human waste. In this case the patient's beliefs and culture prevented an effective role reversal.

Face-saving Techniques

Persons who react to illness as in conversion reactions and factitious disorders often have no way to give up their symptoms without tacitly admitting that they were psychogenic, thereby proving skeptics correct.[7] Many of these patients have difficulty viewing their problem from a psychological perspective and are averse to psychiatric treatment. Techniques that offer patients a face-saving alternative, especially after confrontation has proved ineffective or humiliating, may be extremely useful. Face-saving approaches include biofeedback, relaxation training, and self-hypnosis. Although some patients may protest that these techniques only work for psychological problems, patients find them more acceptable when used in the context of a medically oriented approach and when accompanied by education that these interventions can

work with conditions that are seemingly purely organic in origin such as cancer pain.

For these techniques to work, the physician must not feel obligated to confront patients with the fact that their problems are purely psychological in origin. This approach often accomplishes little except producing anger that results in the patient searching for a new care giver. Instead, the physician informs the patient that there is no major or irreversible illness, but that the suffering is nevertheless real. The physician can then suggest various techniques to help the patient gain control of the symptoms.

Case Example 8

The patient, a 30-year-old woman, was evaluated at an epilepsy center with simultaneous electroencephalographic telemetry and video observation for her three-year history of medically refractory seizures. Previous evaluations had suggested the diagnosis of pseudoepileptic seizures. She vehemently refused psychiatric treatment. When her evaluation at the center confirmed the diagnosis of pseudoepileptic seizures, she was offered a face-saving way to control her symptoms. She was told that although there were no definite electrical abnormalities associated with her seizures, she could learn a technique called biofeedback that would help her gain control of her brain-wave patterns and prevent her seizures. Over the course of a ten-week program, her seizure frequency was reduced from three per week to zero.

Discussion

Solution-oriented approaches can work with a variety of patients. The techniques do not always work—as demonstrated by case 7—and must be used selectively with an awareness of individual circumstances. For example, in many losses reframing is not a reasonable alternative to grieving.

Nonetheless, these techniques can be extremely useful for many patients and are readily applied. In some instances, these kinds of techniques may help shorten hospital stays or decrease the frequency of office visits.[8,9] Although some of the examples given involved psychiatric consultants, primary care physicians could have used all of the interventions. They build on an empathic understanding of patients' experience rather than an investigation of their psychological development. Used with other interventions such as reassurance and clear communication, they help patients feel more in control at times when their disease may make them feel helpless.[10] In an era when physicians are urged to conserve resources, these techniques may help while at the same time providing a sense of collaboration.

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Biomedical Science

Human T-Lymphotropic Virus Types I and II

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Human T-lymphotropic virus types I (HTLV-I) and II (HTLV-II) are members of a family of four known retroviruses that are oncogenic as opposed to cytopathic. This family includes HTLV-I and -II, bovine leukemia virus, and simian T-cell leukemia virus. The two types of HTLV are closely related, and for more than a decade we have been aware of the presence of these viruses in humans. In the first part of this article I summarize recent epidemiologic and clinical findings related to the presence of HTLV-I and -II in the Americas. In the second part, I discuss how these viruses may regulate themselves and how in turn they might cause leukemia and neurologic disease in humans.

(Rosenblatt JD: Human T-lymphotropic virus types I and II. West J Med 1993 Apr; 158:379-384)

Adult T-cell leukemia or lymphoma (ATL) (Figure 1) was the first human malignant neoplasm linked directly to a retrovirus, human T-lymphotropic virus type I (HTLV-I), by the discoveries of Poiesz, Gallo, and Yoshida. The epidemiologic and molecular association of HTLV-I with ATL is clear. In addition to ATL, this unique virus is associated with a slow neurologic disease, formerly known as tropical spastic paraparesis and now known as HTLV-I–associated myelopathy. Virtually all persons with ATL have antibodies to HTLV-I. The virus can transform T lymphocytes in vitro, suggesting that it may play an initiating role in tumor formation in vivo. This virus does not carry a transduced human oncogene and, in fact, does not integrate adjacent to particular human oncogenes with any precision. In different forms of leukemia the site of HTLV-I integration is random, but within a given patient the site of integration of this retrovirus is unique. This tells us that the malignant process arises from a single virally infected cell but that the cell has undergone changes related directly and indirectly to viral infection that render the cell malignant.

In the case of HTLV-associated myelopathy, epidemiologic findings are the primary evidence for viral involvement. Virtually all persons in endemic areas who have a characteristic chronic spastic paralysis, affecting primarily the lower extremities but also resulting in sphincter incontinence, have antibodies to HTLV-I. The virus has been isolated from both the blood and cerebrospinal fluid of these patients. I have studied a familial cluster of this virus in a Mashadi Iranian family in Israel. Several members of the family were infected with HTLV-I, resulting in leukemia in one person and, in another branch of the family, three members in whom HTLV-associated myelopathy developed. This type of familial clustering tells us that either the virus is different or the familial response to this virus may have predisposed certain persons to the development of complications of viral infection. Perhaps 95% of infected persons, however, will have no known clinical consequences.

Recent evidence indicates that human T-lymphotropic virus type II (HTLV-II) may also cause a neurologic disease with symptoms similar to those of HTLV-associated myelopathy. I recently saw a 54-year-old man who was bisexual and had a history of intravenous drug use. He had a 20-year history of progressive leg weakness, initially presenting as paresthesias, that progressed to severe weakness, urinary incontinence, and finally paraparesis that confined him to a wheelchair. On physical examination he had marked spastic weakness of both lower extremities. He had 3+ knee jerks bilaterally and pronounced clonus, as well as a bilateral Babin-

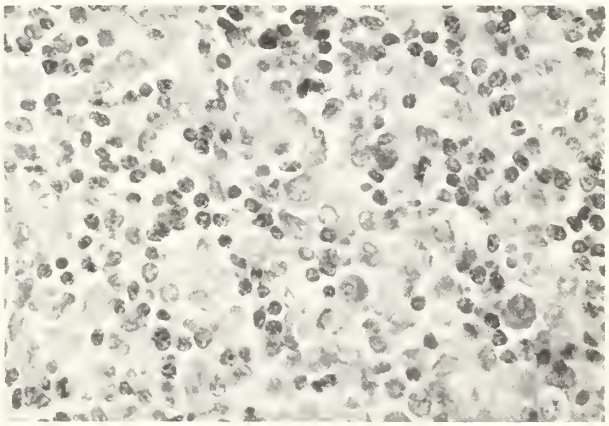

Figure 1.—The photomicrograph was taken of a lymph node from a Japanese patient with adult T-cell leukemia or lymphoma associated with human T-lymphotropic virus type I (hematoxylin-eosin stain) (courtesy of Dr Masao Tomanaga, Atomic Disease Institute, Nagasaki, Japan).

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ABBREVIATIONS USED IN TEXT

ATL = adult T-cell leukemia or lymphoma
CAT = chloramphenicol acetyltransferase
HIV-1 = human immunodeficiency virus type 1
HTLV-I, -II = human T-lymphotropic virus type I, II
mRNA = messenger RNA
PTHrP = parathyroid hormone-related protein promoter

ski's reflex. Other findings were consistent with but not diagnostic of HTLV-associated myelopathy, including mild lymphocytosis of the cerebrospinal fluid. Similar to persons with multiple sclerosis, this patient had oligoclonal banding of antibodies in the cerebrospinal fluid. In the case of this particular patient, HTLV-II rather than HTLV-I was identified in his peripheral blood lymphocytes using a polymerase chain reaction on four separate occasions. This is apparently an index case. A similar case was reported in Florida and two other cases were reported in New Mexico in which persons infected with HTLV-II had a paralytic illness similar to this disorder. The patients reported from New Mexico also had cerebral and cerebellar atrophy in one case and cerebellar ataxia thought to be due to infection with HTLV-II. Thus, HTLV-I and -II apparently elicit similar neurologic sequelae in predisposed persons.

In the case of HTLV-II, the less well-known member of this viral family, most people known to be infected are asymptomatic carriers, although some will have a mild T-cell lymphocytosis. Some users of injection drugs who are infected with HTLV-II have had elevated creatine kinase levels, apparently of muscle origin. Four cases of lymphoid malignancy have been linked to HTLV-II, and this appears to be a rare complication of the virus. As opposed to HTLV-I, HTLV-II appears to preferentially infect $CD8^+$ cells; malignant tumors linked to HTLV-II generally have been of the $CD8^+$ T-suppressor cell phenotype, whereas ATL due to HTLV-I almost always involves $CD4^+$ T-helper cells.

Clinical consequences of HTLV-I infection in addition to HTLV-associated myelopathy and ATL have been reported anecdotally. These include polymyositis with or without associated myelopathy, uveitis, and HTLV-I–associated arthropathy, frequently occurring in association with myelopathy. In addition, a growing number of cases have been observed in Jamaica of a pediatric illness, currently designated as "infectious dermatitis," that is associated with recurrent skin infection with staphylococcal and streptococcal bacteria; these cases appear to correlate with HTLV-I seropositivity. The role of HTLV-I in these disorders is poorly understood. A summary of known and suspected sequelae of HTLV-I and -II infection is presented in Table 1.

Since 1985, blood banks in the United States have been screening the blood supply for the prevalence of HTLV-I and -II. In a recent study by Lee and colleagues that looked at almost 500,000 blood donors across the United States in geographically disparate areas, the overall seroprevalence of infection with HTLV-I and -II was estimated to be 0.04%. With the use of discriminatory DNA amplification techniques, 34 of 65 persons (53%) seropositive by serologic reagents derived from HTLV-I were actually infected with HTLV-II. This is surprising because this is one of the few examples in which testing for antibodies using the proteins of one virus, HTLV-I, identifies a large proportion of patients who were actually infected with a related virus, HTLV-II. This is due to the homology between the antigenic proteins of these two viruses. The transmembrane protein P21e is highly antigenic and has a high degree of homology in both viruses. The envelope protein also has a high degree of homology but is somewhat less antigenic; the structural Gag proteins p24 and p19 are highly antigenic and have extensive homology. In the United States, cases of HTLV-II infection are generally associated with intravenous drug use, except in specific ethnic groups (discussed later). In contrast, most persons infected with HTLV-I come from known endemic areas or have had sexual contact with persons from endemic areas. In Lee and associates' study, the vast majority of people interviewed who gave a history of either intravenous drug use or a sexual partner who engaged in intravenous drug use were infected with HTLV-II. Other studies indicate that most seropositive American injection drug users are infected with HTLV-II.

TABLE 1.—*Clinical Manifestations of Infection With Human T-Lymphotropic Virus Type I (HTLV-I) and Type II (HTLV-II)*

- HTLV-I
  - Adult T-cell leukemia or lymphoma (ATL)
  - Pre-ATL or asymptomatic lymphocytosis
  - Chronic ATL
  - Smoldering ATL
  - Acute-type ATL
  - HTLV-I–associated myelopathy
    - HTLV-I–associated arthropathy
    - Uveitis
    - Polymyositis?
    - Sjögren-like syndrome?
  - Infectious dermatitis in children
  - Alveolitis or pulmonary disorders?
- HTLV-II
  - $CD8^+$ T-suppressor cell lymphocytosis or leukemia
  - "Atypical" hairy cell leukemia?
  - Myositis or abnormal creatine kinase levels
  - HTLV-II–associated neurodegenerative diseases
    - Spastic paraparesis
    - Cerebellar or cerebral atrophy?

Known endemic groups for HTLV-II infection include the Guaymian Indians in Panama, with a 5% to 10% rate of infection, and New Mexico American Indians, in whom a 3% rate of infection was found. Higher rates of HTLV-II infection have also been reported in the Kayapo Indians in Amazonia, Brazil. An interesting report suggests that spider monkeys and capuchin monkeys from South and Central America may be infected with

HTLV-II. Although most Africans and African primates are infected with HTLV-I, Indian populations in the western hemisphere may have been exposed primarily to HTLV-II. The reason for this unusual geographic separation of two closely related viruses is unclear.

An unusual feature of HTLV-I and -II biology relates to the relatively high degree of conservation between different HTLV-I isolates. This is especially striking in contrast to the known variability of isolates of human immunodeficiency virus type 1 (HIV-1). The env sequences from numerous HTLV-I isolates from various areas of Melanesia, Japan, Iran, the Caribbean, and Africa have been compared by Gessain and others. These studies indicate that African and Japanese isolates may be as much as 97% to 99% conserved, whereas Melanesian HTLV-I sequences obtained from geographically isolated tribes in New Guinea may differ by as much as 7% to 8% in the env region from prototypic Japanese isolates. Human T-lymphotropic virus type II may also exist in two closely related subtypes, as defined by consistent differences in restriction maps between isolates. The two original HTLV-II isolates, HTLV-II Mo and HTLV-II NRA, initially characterized by Chen, each correspond to a different subtype, now designated HTLV-II_A and HTLV-II_B, as defined by a study of numerous HTLV-II isolates. The overall degree of genetic heterogeneity between HTLV-II subtypes is not known. Nevertheless, compared with HIV-1, the degree of sequence conservation among HTLV-I and HTLV-II isolates is striking and may reflect lower levels of viral replication or perhaps a different replication strategy.

Pathogenesis and Molecular Biology of HTLV-I and -II

The unique regulatory properties of HTLV-I and -II provide clues to their pathogenesis. The genomic organization and regulatory proteins of HTLV-I and -II are remarkably similar. These viruses, which do not contain an oncogene, are unique in that the 3′ end of their genome contains sizable open reading frames that encode at least two proteins (Figure 2). One is a transcriptional regulator called Tax; the other is a posttranscriptional regulator called Rex that actually regulates the use and transport of viral messenger RNA (mRNA). Both may play a role in pathogenesis and in the viral life cycle. Recently investigators have obtained evidence that additional proteins may also be encoded by the 3′ end of the genome through alternative splice sites, although these are as yet poorly understood, and their role, if any, in the viral life cycle is still unknown.

The Tax protein is a nuclear phosphoprotein that is responsible for enhanced viral RNA transcription from the viral promoter, and HTLV-I and -II will not replicate without Tax. The viral requirement for Tax was first pointed out by Chen, who noted that HTLV-II proviral mutants in Tax made little mRNA. Much evidence suggests that Tax does not limit its effects as a *trans*-activator to viral genes but can actually *trans*-activate a variety of cellular genes. This may be an important clue to pathogenesis by the HTLV viruses. If the viral promoter for HTLV-II, the long terminal repeat, is linked to a bacterial indicator gene such as chloramphenicol acetyltransferase (CAT), expression from that promoter in mammalian cells depends on two processes. First, RNA must be transcribed, and measurable RNA transcription occurs from the viral long terminal repeat only in the presence of Tax. In addition to transcription, expression of the indicator CAT protein is also dependent on the presence of the posttranscriptional regulator, Rex. Although RNA is abundant, its expression is low in the absence of Rex because of the role Rex plays in viral mRNA processing. It appears to facilitate export of full-length gag or pol and partially spliced env mRNA from the nucleus to the cytoplasm.

The early response gene, *egr*-1, is an example of a cellular gene dysregulated by Tax in HTLV-I–infected cells. It is a zinc-finger DNA-binding protein and is thought to be a transcription factor important in early proliferation. Another member of this family of genes is the Wilms' tumor gene. If the promoter of *egr*-1 is linked to a CAT indicator gene, it has been shown that transcription from the *egr*-1 promoter increases substantially, about 20-fold or more by HTLV-I Tax and almost 40-fold by HTLV-II Tax. This may account for a constitutive expression of *egr*-1 in cells infected with HTLV-I and -II.

Another example of cellular gene dysregulation that may actually contribute to the malignant phenotype is that of the parathyroid hormone-related protein promoter (PTHrP), a protein with substantial amino acid homology at its amino terminus to human parathyroid hormone. Cells infected with HTLV-I constitutively express PTHrP, as do ATL cells. In human tumors such as squamous cell carcinoma of the lung, overexpression of this protein may lead to humoral hypercalcemia. Hypercalcemia will develop in more than 70% of persons with ATL. Studies have shown that if the promoter for the PTHrP gene is linked to CAT and studied, it is *trans*-activated

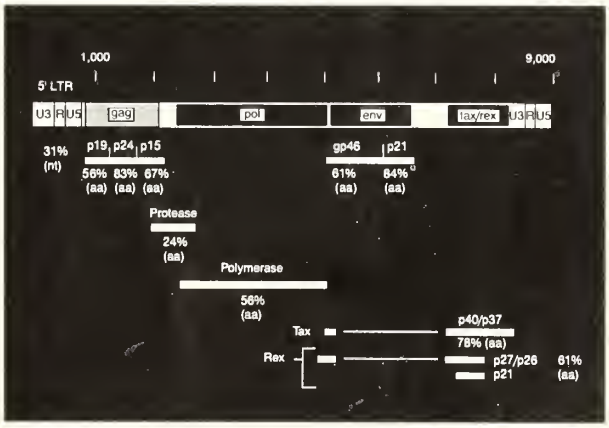

Figure 2.—The diagram shows the genomic organization and nucleic or amino acid homology of the human T-lymphotropic virus types I and II. Known coding regions and protein products for **gag** (structural), **pol** (reverse transcriptase, integrase, ribonuclease H), **env** (envelope), and the transregulatory proteins **tax** and **rex** are indicated beneath a schematic diagram of the complete genome. Nucleic acid homology is indicated by **(nt)**, amino acid homology by **(aa)**.

more than 100-fold by Tax of either HTLV-I or -II. This induction of PTHrP appears to be specific to T cells, as HTLV-infected B-cell lines do not overproduce PTHrP. Hence, Tax effects on the expression of hypercalcemic factors such as PTHrP may account for the hypercalcemia often observed in patients with ATL.

The Tax regulatory protein may also act through a variety of transcriptional pathways to change the phenotype of an infected cell. For example, Tax may increase the expression of the interleukin-2 receptor-α (*IL2Rα*) chain genes. Cells infected with ATL and HTLV-I express a high concentration of the high-affinity interleukin-2 receptor on their surface. In this case, Tax *trans*-activates the *IL2Rα* chain promoter through interaction with a transcription factor known as NF-κB. We and others have identified various oncogenes, such as *egr*-1 and c-*fos* and cytokine genes such as *GMCSF*, whose transcriptional regulation is changed by the presence of Tax. Soluble Tax has been shown to possibly enter cells and cause transcriptional effects similar to those seen with the intracellular production of Tax. Therefore, Tax may be highly involved in the genesis of the malignant phenotype. Possible contributions of Tax to the malignant phenotype are outlined in Figure 3. Experiments indicate that Tax, expressed in normal T cells under the control of a herpes Saimiri vector, may be capable of transforming normal T cells. Hence, many investigators think that the myriad cellular effects of Tax may contribute to the pathogenesis of leukemia. In addition, workers at the National Institutes of Health have reported a high frequency of cytotoxic T cells directed against Tax in the central nervous system and blood of patients with HTLV-I–associated myelopathy. Therefore, the immune response to the Tax protein may be involved in the pathogenesis of myelopathy.

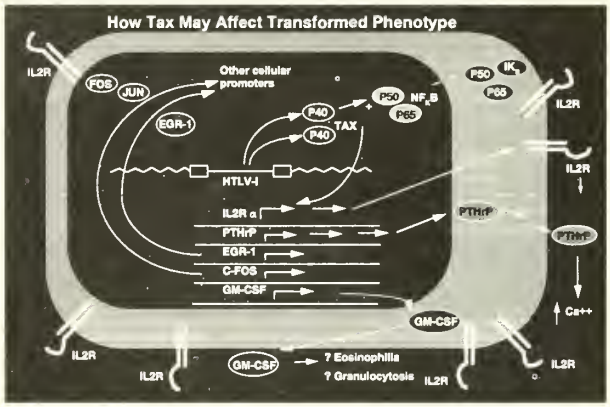

Figure 3.—The effects of Tax on the transformed T-cell phenotype are shown. Cellular genes whose regulation is positively altered by Tax include the *IL2Rα* chain of the high-affinity cellular receptor for interleukin-2; parathyroid hormone-related protein promoter **(PTHrP)**, a mediator of humoral hypercalcemia; the cytokine **GM-CSF**; and a variety of transcription factors, including *egr*-1, c-*fos*, and **NF$_\kappa$B**.

We know from epidemiologic studies that infection with HTLV does not generally result in the formation of a malignant neoplasm, and four or five decades may pass following childhood infection before ATL arises. Therefore, secondary events appear to be important in leukemogenesis. These secondary events involve particularly translocations in chromosome 14. Of note, chromosome 14 contains the T-cell receptor α-chain coding sequences. Translocations involving chromosome 14 are often found in ATL cells, but not in carriers of HTLV-I. No characteristic translocation leading to ATL has been identified, however. Perhaps a variety of cytogenetic lesions may lead to the development of ATL in a previously infected cell.

The Rex protein is a posttranscriptional regulator of RNA expression in both HTLV-I and -II and is encoded on the same mRNA as Tax. It occurs in both phosphorylated and nonphosphorylated forms. Work with HTLV-II has shown that Rex is phosphorylated on a serine residue and that only the phosphorylated Rex can bind to viral mRNA target sequences. Genetic studies show that while Tax acts to increase RNA transcription from the viral promoter, Rex acts after RNA has been transcribed to increase expression and, in fact, increases nuclear to cytoplasmic export of that mRNA. Studies have demonstrated a decrease in cytoplasmic viral gag and env mRNA in the absence of Rex. The region through which Rex acts has been mapped to a 225-nucleotide segment downstream from the RNA transcriptional start site in the HTLV-II viral long terminal repeat (Figure 4).

To understand how Rex may mediate its function, Yip studied recombinant Rex produced from a baculovirus expression system and showed that Rex binds specifically and directly to a portion of RNA response element that we had mapped genetically. This can be demonstrated using either a gel retardation or an RNA immunobinding

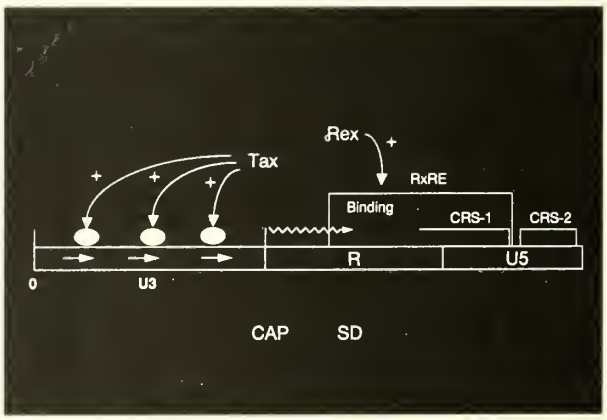

Figure 4.—The proteins Tax, Rex and *cis*-acting elements in the viral long terminal repeat (LTR) regulate the expression of human T-lymphotropic virus types I and II. Tax appears to interact with DNA-binding proteins, which bind to imperfect 21-base pairs repeated enhancer elements in the viral LTR, to increase the rate of transcription **(arrows)**. Rex binds to a *cis*-acting regulatory element, the Rex response element **(RxRE)**, in transcribed messenger RNA (mRNA), and increases the net export of full-length gag or pol mRNA and partially spliced env mRNA. Rex may act to relieve constraints on mRNA export conferred by two *cis*-acting repressive elements **(CRS-1** and **CRS-2)** downstream from the Rex binding element. Of note, the 5′ splice donor site **(SD)** is contained within the Rex binding element. The **CAP** site is the start for viral messenger RNA transcription.

TABLE 2.—*Parallel Evolution of Regulatory Mechanisms in Human Retroviruses*

Human Immunodeficiency Virus Types 1 and 2		*Human T-Lymphatrapic Virus Types I and II*	
Regulatory Protein	*Regulatory Mechonism*	*Regulatory Pratein*	*Regulatory Mechanism*
Tat	RNA binding	Tax	No direct binding
	Increased messenger RNA (mRNA) transcription		Increased mRNA transcription
	Increased mRNA elongation		Nuclear localization
	Nuclear localization		
Rev	RNA binding	Rex	RNA binding
	Increased gag/env expression		Increased gag/env expression
	Decreased Tat/Rev expression		Decreased Tax/Rex expression
	? Decreased transcription		? Decreased transcription
	Cannot substitute for Rex		Can substitute for Rev
	Nucleolar localization		Nucleolar localization
	Phosphorylated		Phosphorylated form binds RNA
	cis-Acting repressive sequences (CRS) in gag/pol and env mRNA		CRS identified in the long terminal repeat

assay. The RNA migrates normally in the gel, but in the presence of increasing concentrations of Rex more RNA is bound and RNA migration is retarded. The Rex protein binds to its cognate RNA recognition element and requires a specific sequence and RNA secondary structure. We mapped the recognition element and found that, with 100% binding in a wild-type recognition element, specific Rex binding to a 425-base pair transcript from the long terminal repeat can be decreased by more than 90% by altering the Rex binding element by only two nucleotides. Similarly, for Rex to bind efficiently, the splice donor site, which is the site at which RNA is spliced and processed, must also be intact.

Once HTLV-I produces mRNA, the Rex protein can then bind to and alter the fate of that RNA. This may occur as a consequence of Rex binding, following which more unspliced gag or pol mRNA is exported from the nucleus and more virus can be produced. Because splicing occurs at the 5′ splice site and is initiated by binding of an RNA-protein complex called the U1-SnRNP, the fact that Rex may also interact directly with the splice donor site suggests it may interfere directly with the initiation of splicing. Similarly, Rex may relieve the effect of certain negative regulatory sequences in the virus downstream from the sequences that bind Rex. These sequences, called *cis*-acting repressive sequences, are present in both HTLV-I and -II and interact with cellular proteins that govern mRNA exit from nucleus to cytoplasm. Similar regions have been identified in HIV-1. It remains to be determined whether Rex can alter mRNA transport, whether Rex interferes directly with the process of splicing, or whether both mechanisms are affected by Rex.

The Rex protein plays a role in the viral life cycle by altering the use and transport of certain viral RNA. It can actually substitute for an HIV-1 protein called Rev, which has essentially the same function. Rex may affect the splicing, posttranscriptional regulation, or both, of selected cellular mRNA in addition to viral mRNA. Its effects on cellular mRNA, however, are not yet known. A better understanding of the two proteins, Rex and Rev, may provide us with new approaches to treating both HTLV-I and HIV-1 infection.

The two major classes of human retroviruses, HIV (types 1 and 2) and HTLV (types I and II), appear to have independently evolved parallel strategies for replication in the host and for possible evasion of the immune system (Table 2). Both have proteins that increase the overall levels of viral RNA transcription: Tat in the case of HIV-1 and -2 and Tax in the case of HTLV-I and -II. In addition, both have evolved proteins that regulate how the RNA is used and transported in the cell. In the case of HIV, Rev increases expression of the structural and envelope proteins of the virus; this function is performed by Rex in the case of HTLV-I and -II. In addition, both Rev in HIV and Rex in HTLV-I and -II may actually inhibit their own expression and that of the other *trans*-acting regulatory proteins. The comparative study of Tat, Tax, Rev, and Rex has yielded important new insights into the retroviral life cycle and pathogenesis.

These molecular biologic studies are providing an increased understanding of how these viruses may cause dysregulation of the human T cell that leads to the formation of a malignant neoplasm. These studies may also shed light on the development of neurologic diseases as a consequence of HTLV-I and -II infection.

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Conferences and Reviews

Antiplatelet Therapy—Part I

SCOTT H. GOODNIGHT, MD; BRUCE M. COULL, MD; JOHN H. McANULTY, MD;
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We summarize current information about aspirin and other antiplatelet drugs in patients with cardiac and vascular disease. For each indication, we briefly summarize the rationale for the use of antiplatelet therapy and describe the findings of relevant clinical trials. We propose recommendations for the use of these agents in clinical practice. Part I covers the use of antiplatelet therapy for the primary and secondary prevention of myocardial infarction, coronary thrombolysis, unstable and chronic stable angina, and coronary artery-saphenous vein bypass grafts. In part II we review the use of antiplatelet agents in coronary angioplasty, atrial fibrillation, artificial cardiac valves, stroke, and peripheral vascular disease.

(Goodnight SH, Coull BM, McAnulty JH, Taylor LM: Antiplatelet therapy—Part I. West J Med 1993 Apr; 158:385-392)

The drugs used to inhibit platelet function are frequently prescribed in the United States today. The popularity of aspirin and other antiplatelet agents stems from a growing number of studies showing benefit in patients with atherosclerotic vascular disease and from the fact that the risks of therapy are considered by many to be low. Articles about antiplatelet therapy have been voluminous and often contradictory, making a careful and thoughtful assessment of the indications, risks, and benefits of antiplatelet therapy challenging at best for practicing physicians.

We concisely but critically review the indications and optimal use of antiplatelet therapy for patients with vascular and cardiac disease. When more information or discussion is required, readers are directed to several excellent reviews in which antiplatelet and other antithrombotic therapies are discussed in detail.[1-19]*

For each category of disease—for example, the secondary prevention of coronary heart disease—we discuss the rationale for the use of antiplatelet therapy, after which we briefly assess the major clinical trials that have strongly influenced recommendations for therapy. When appropriate, alternative forms of therapy, such as anticoagulants, are included. Finally, a set of recommendations has been formulated based on the information that is currently available.

While many of these recommendations may be almost universally accepted, others are controversial. In any event, each of the major trials is cited as well as analyses of these trials by others, allowing readers to probe more deeply into the subject with relative ease.

*See also "Use of Antiplatelet Agents in the Management of Thrombotic Disorders," by L. A. Harker, MD, on pages 426-427 of this issue.

Antiplatelet Agents

Aspirin

Aspirin's antithrombotic effects are thought to lie in its ability to inhibit platelet aggregation (but not platelet adhesion) by blocking the action of platelet cyclooxygenase and thereby reducing the cellular synthesis of thromboxane A_2.[20,21] Unfortunately, aspirin also inhibits endothelial cell prostaglandin synthesis and therefore reduces the release of prostacyclin. Because prostacyclin is thought to be a potent antiplatelet agent in vivo, this aspect of aspirin's action might lessen its therapeutic usefulness.

There seems to be little question that aspirin can be an effective antithrombotic agent.[22] Questions remain, however, as to the optimal dose, formulation, and schedule of administration for the prevention of thromboembolism in patients with vascular or cardiac disease. For example, clinical trials have been conducted using doses of aspirin ranging from 30 to more than 3,000 mg daily, all showing apparent benefit.

A surrogate marker for the possible efficacy of aspirin as an antithrombotic agent may be the relative inhibition of thromboxane compared with prostacyclin synthesis. At least on theoretic grounds, an optimal dose of aspirin would maximally inhibit platelet thromboxane synthesis but completely spare prostacyclin. Many studies have been done to examine this hypothesis. In general, it appears that lower doses of aspirin—60 to 325 mg a day—may be more effective than higher doses, less frequent administration (daily or every other day) may be better than several daily doses, and the use of very-low-dose sustained-release preparations may be the most effective.[23-27] Not all would concur with this interpretation of

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This is part I of a two-part article. Part II will be published in the next issue of *The Western Journal of Medicine*.

the data, however, particularly in the case of cerebrovascular disease in which a higher dose of aspirin might be superior to lower doses.[28] The incidence of bleeding complications may also be lower, but not absent, with smaller doses of aspirin.[29] In the final analysis, however, high-quality, randomized, controlled clinical trials will be necessary to determine the optimal regimens for aspirin therapy.

An interesting and possibly important facet of platelet function is that platelet reactivity may vary depending on the time of day. Platelet reactivity has been reported to be considerably increased in the early morning hours, although the mechanisms responsible for this finding are not known. This increase in activity has been associated with an increased risk of myocardial infarction and sudden cardiac death.[30] Ischemic stroke has also been reported to be more common in the morning.[31] Of interest, this increase in platelet reactivity may be suppressed by low doses of enteric-coated aspirin.[32]

Whether there is a sex difference in response to aspirin therapy remains unknown. Some studies have suggested that men have more platelet reactivity than women. It is not clear whether the doses of aspirin must be adjusted to accommodate these possible differences.[33,34]

As mentioned, a multitude of aspirin dosage schedules have been employed in the clinical trials published to date. It is reasonable to follow the dictates of the clinical trials in making recommendations for antiplatelet therapy, but in situations where optimal therapy is unclear, a general recommendation for aspirin therapy could include either 325 mg daily[35] or 325 mg every other day.[36]

Ticlopidine Hydrochloride

Ticlopidine is a thienopyridine derivative that has been shown to inhibit platelet aggregation, perhaps by blocking the exposure of glycoprotein IIb-IIIa fibrinogen binding sites on platelets.[37] Ticlopidine hydrochloride has been shown to be an effective antiplatelet agent in several clinical trials, but possible drawbacks of this therapy include a low incidence of neutropenia (<1% but usually reversible), an increase in serum cholesterol levels (about 10%), diarrhea (as many as 20% of patients), and a substantially greater cost than for aspirin.[37-40] Recently, a fatal syndrome resembling thrombotic thrombocytopenic purpura or hemolytic-uremic syndrome has been reported in four patients taking ticlopidine, with the symptoms occurring two to three weeks after starting therapy.[37,41] Ticlopidine has now been approved for use in patients with transient ischemic attacks who cannot tolerate aspirin. Additional clinical trials are warranted to compare ticlopidine use with that of aspirin to determine their relative efficacy and safety and to learn whether combining the two agents may be safe and provide increased therapeutic benefit.

Other Agents

Other antiplatelet agents that have been thoroughly studied include dipyridamole and sulfinpyrazone.[25,26] Most investigators have concluded that these agents are not as effective as aspirin, and their use has gradually diminished over the past decade.[42]

Primary Prevention of Myocardial Infarction

Rationale

Myocardial infarction commonly results from acute coronary artery occlusion by platelet thrombus at the site of a ruptured atherosclerotic plaque.[43] Unfortunately, many patients with acute coronary artery occlusion have no warning symptoms, which precludes early diagnosis and treatment. Antiplatelet therapy has been shown to be successful in reducing platelet-mediated thromboses in various experimental models.[44] Platelet inhibitory therapy, such as low-dose aspirin, is relatively safe and inexpensive.

Major Clinical Trials

The Physicians' Health Study was a placebo-controlled, blinded, randomized clinical trial involving 22,071 male physicians.[36] Participants received aspirin, 325 mg every other day, or a placebo tablet. Those physicians older than 50 years who were taking aspirin had a statistically significant 44% reduction in the first occurrence of fatal and nonfatal myocardial infarction, although overall death rate from cardiovascular causes was not changed (relative risk = 0.96). The relative risk of fatal and nonfatal myocardial infarction with low-dose aspirin therapy was 0.56 ($P << .01$). There was a small but not significant increase in the incidence of stroke, mainly because of the subgroup with hemorrhagic stroke (relative risk = 2.14, $P = .06$).

The British Doctors' Trial included 5,139 physicians whose ages ranged from 50 to 78 years.[45] This trial was randomized but was not placebo controlled and extended for six years. Treated subjects received 500 mg of aspirin a day, whereas the controls were asked to refrain from taking aspirin. A trend (nonsignificant) was found for a decrease in the myocardial infarction incidence. The statistical confidence intervals did not exclude a 25% reduction in the incidence of myocardial infarction by aspirin. Total mortality was 10% lower in the aspirin group, but this did not reach significance. The incidence of disabling strokes was slightly but significantly increased in the aspirin-treated patients ($P = .05$).

Considering both primary prevention trials together, there was a significant reduction in the incidence of nonfatal myocardial infarction of about a third ($P << .01$).[46] There was no significant difference in the number of cerebrovascular events, but a nonsignificant increase in the incidence of disabling stroke was found. Neither trial, nor the trials taken together, had the power to assess the effect of aspirin therapy on overall mortality.

The Nurses' Prospective Cohort Study was a nonrandomized trial of a group of 87,678 registered nurses ranging in age from 34 to 65 years and free of baseline disease for six years.[47] Women who reported taking one to six aspirin tablets per week (but not more) had a relative risk

of a first myocardial infarction that was 0.68 ($P<.01$) compared with women who did not take aspirin. When other risk factors for coronary artery disease were included in the analysis, the relative risk in the aspirin group was 0.75 ($P<.05$). The risk reduction for women 50 years of age or older was 0.61 ($P<.01$). There was no alteration in the risk of stroke.

Recommendations

- Men older than 50 years who have substantial coronary risk factors—such as a strong family history of coronary artery disease, hyperlipidemia, or diabetes mellitus—should take one 325-mg aspirin tablet every other day.
- Men older than 50 without risk factors should not take aspirin on a regular basis. Aspirin therapy, however, can be considered for men who are younger than 50 years who have strong coronary risk factors, although there is as yet no direct evidence from clinical trials of benefit from this therapy.
- Women older than 50 years who have coronary risk factors may benefit from taking one tablet daily or one every other day—although benefit has not yet been shown in a prospective, randomized clinical trial.
- Aspirin therapy should not substitute for the aggressive management of other coronary risk factors such as smoking, hyperlipidemia, lack of exercise, diabetes mellitus, or systemic hypertension.

Secondary Prevention of Myocardial Infarction

Rationale

As mentioned in the previous section, platelet-mediated thrombosis is often responsible for acute coronary artery occlusion, and this process may respond to antiplatelet therapy. Moreover, several recent studies have suggested that platelet reactivity and mean platelet volume may be increased in some patients following myocardial infarction and that these findings may predict future coronary artery occlusion.[48-51]

Major Clinical Trials

The Antiplatelet Trialists Collaboration did a meta-analysis of 25 trials of prolonged antiplatelet treatment of patients with a history of coronary artery disease, transient ischemic attacks, or stroke.[35] Data from a total of 29,000 patients were included in the study, of whom 3,000 died. The analysis showed that various regimens of antiplatelet therapy significantly reduced mortality from vascular causes by 15%, the incidence of stroke or myocardial infarction by 30%, and that of overall vascular events by 25%. There was no apparent effect on mortality due to nonvascular causes. The reductions in three separate end points—nonfatal myocardial infarction, nonfatal stroke, and the total number of deaths due to cardiovascular disease—were significant in the antiplatelet treatment groups ($P<<.01$). All-cause mortality was also reduced ($P<<.01$). The authors concluded that higher doses of aspirin conferred no more benefit than 325 mg daily.

The Second International Study of Infarct Survival (ISIS-2 trial) enrolled 17,187 patients in a multicenter study of patients presenting with clinically suspected myocardial infarction who were treated with 1.5 million units of intravenous streptokinase, aspirin (160 mg daily), both, or neither therapies.[52] After five weeks, mortality in the groups receiving aspirin was decreased by 23% compared with placebo ($P<<.01$) and the reinfarction rate was decreased by 50%. The benefit of aspirin therapy was still apparent 15 months later ($P<.01$). No increase in the incidence of cerebral hemorrhage was found in the aspirin-treated patients.

Alternative Treatment

Two clinical trials of high-intensity (international normalized ratio* of 3 to 5) oral anticoagulants, the 60-Plus Reinfarction Study of 1980 and the Norwegian Anticoagulant Study of 1990, showed significant reductions in the incidence of myocardial infarction, stroke, and death in the patients receiving anticoagulants after two to three years of treatment.[54,55]

Recommendations

- Patients presenting with acute myocardial infarction should receive 160 mg of aspirin immediately and daily thereafter while in the hospital. Aspirin should be given whether or not the patient is a candidate for treatment with thrombolytic agents.
- All patients with acute myocardial infarction should receive long-term therapy with 325 mg of aspirin daily, unless there is a contraindication to its use. Aspirin therapy should be continued for at least two years and probably indefinitely.
- Alternatively, patients could be treated with high-intensity warfarin sodium anticoagulation—international normalized ratios of 3 to 4.5—although the increased risk of bleeding may offset some of the benefits of this form of therapy. If there are other indications for anticoagulants (such as dilated cardiomyopathy), then warfarin should probably take precedence over aspirin therapy.

Antiplatelet Therapy After Coronary Artery Thrombolysis

Rationale

A recurrence of thrombosis is a major problem after successful coronary artery thrombolysis and has been found to occur in 5% to 20% of patients.[56] Potent thrombogenic stimuli include residual unlysed thrombus and the surface of the ruptured coronary artery plaque. In addition, a major product of activated platelets, thromboxane A_2, is markedly increased in amount during and after coronary thrombolysis using streptokinase or tissue plasminogen activator.[57,58] An increased concentration of thromboxane metabolites is present in the urine during the procedure and for as long as 48 hours afterwards. The site of platelet activation is unknown but may be the

*The international normalized ratio is a standardized method of reporting prothrombin times to ensure that a uniform intensity of oral anticoagulant therapy is used worldwide.[53]

reperfused coronary artery bed. Antiplatelet therapy might inhibit platelet reactivity and thereby reduce the rate of rethrombosis in the days or weeks following thrombolysis.

Major Clinical Trials

The large multicenter ISIS-2 study involving more than 17,000 patients showed that thrombolytic therapy with streptokinase, when given with aspirin—160 mg daily for a month—resulted in a 42% decline in the number of vascular deaths five weeks later compared with the administration of streptokinase alone ($P << .01$).[52] Aspirin therapy also decreased the rate of nonfatal reinfarction. No increased incidence of bleeding was seen with the combination therapy. The principal findings of the study were unchanged at 15 months.

In the Heparin–Aspirin Reperfusion Trial Study, heparin (a 5,000-unit bolus followed by a continuous infusion) appeared to be a more effective antithrombotic agent than low doses (80 mg) of aspirin when given in conjunction with recombinant tissue plasminogen activator for thrombolysis.[59] Angiograms obtained 7 to 24 hours after thrombolysis showed an 82% patency rate in the patients assigned to receive heparin, compared with 52% in the aspirin group ($P < .01$). In contrast, aspirin therapy was at least as effective as the use of heparin in preventing reocclusion between days 1 and 7 after thrombolysis. A question might be raised, however, as to whether an adequate dose of aspirin was used at the start of the fibrinolytic therapy.

The European Cooperative Study Group examined the effects on infarct size and left ventricular function of the administration of tissue plasminogen activator, aspirin, or heparin.[60] When all three drugs were used, there was a statistically significant 20% reduction in the size of the infarct as reflected in serum enzymes. In addition, the ejection fraction was 2.2% higher in this group ($P < .01$). Only 18 of 47 deaths occurred in patients receiving the three drugs, whereas 29 deaths occurred in the group of patients receiving only aspirin or heparin. The 51% reduction in mortality failed to reach statistical significance, however, because of the small number of patients enrolled in the study.

Recommendations

- Aspirin, 160 to 325 mg, should be given as soon as possible when a diagnosis of acute myocardial infarction is made and thrombolytic therapy is being considered.
- Intravenous heparin, given first as a bolus and then followed by a continuous infusion, should be administered along with thrombolytic therapy.
- If surgical revascularization is not required, then the use of aspirin, 325 mg daily, is recommended indefinitely for the secondary prevention of myocardial infarction. There are no data available as yet to suggest that aspirin therapy reduces the incidence of late coronary artery reocclusion following thrombolysis.

Unstable Angina

Rationale

As shown by coronary angioscopy, the pathogenesis of unstable angina is thought to involve the formation of platelet thrombi on the surface of disrupted atherosclerotic plaques, which intermittently produces vascular occlusion.[61] The activation of platelets may also reduce blood flow by the release of vasoconstrictors such as thromboxane A_2, whose effects may be augmented by a loss of vasodilators such as prostacyclin or endothelium-derived relaxing factor from the damaged vascular surface.[62] Because platelets appear to play an important role in the pathogenesis of unstable angina, therapy to inhibit platelet aggregation seems appropriate and rational.

Major Clinical Trials

The Veterans Administration Cooperative Study was a multicenter, double-blind, randomized, placebo-controlled trial that evaluated 1,266 men with unstable angina.[63] Patients were given buffered aspirin, 325 mg daily, or placebo for 12 weeks. The incidence of nonfatal myocardial infarction or death was 51% lower in the aspirin-treated group ($P < .01$), and total mortality was also decreased by 51% ($P = .05$). The benefits of aspirin therapy persisted for the ensuing year.

The Canadian Multicenter Trial examined 555 (74% male) patients with unstable angina who received 325 mg of aspirin four times a day, sulfinpyrazone, 200 mg four times a day, both drugs, or placebo for 18 months.[64] The relative risk of death due to cardiac disease and of nonfatal myocardial infarction in the patients receiving aspirin was reduced by 51% ($P < .01$). A risk reduction of 71% was found when death from cardiac disease alone or from any cause was considered ($P < .01$).

The Montreal Heart Institute Trial compared the administration of aspirin, 325 mg twice a day, heparin, 1,000 units per hour, aspirin plus heparin, or placebo in 479 patients with unstable angina.[65] Patients were entered into the study eight hours after their last episode of pain and were treated for six days. Aspirin use decreased the rate of myocardial infarction by 72% ($P < .05$) compared with 89% for heparin ($P < .01$). The combination of heparin plus aspirin was no better than either alone, but resulted in an increased incidence of bleeding.

The Ticlopidine Trial was an open, non–placebo-controlled trial that studied 652 patients who were given either conventional therapy (without aspirin) or conventional therapy plus ticlopidine in a dose of 250 mg twice a day.[66] Treatment was begun within 40 hours, and patients were observed for six months. The incidences of death due to cardiovascular events and nonfatal myocardial infarction combined were reduced from 13.6% to 7.35% in these patients, a risk reduction of 46.3% ($P < .01$). The relative risk of dying of cardiovascular disease alone was 0.47, which did not reach significance ($P = .14$).

The RISC Group [Research on Instability in Coronary Artery Disease] studied 796 men with unstable angina or non–Q-wave myocardial infarction in a double-

blind, placebo-controlled trial for a year.[67] Treatment consisted of 75 mg of aspirin taken orally with or without five days of intermittent intravenous heparin therapy. In this study, the use of aspirin reduced the risk of myocardial infarction and death. After five days, the risk ratio was 0.43 ($P<.05$); by one month it was 0.31 ($P<<.01$), and after three months it was 0.36 ($P<.01$). This trial was unique in that moderately low doses of aspirin (75 mg) were used.

Finally, aspirin in a dose of 75 mg daily or placebo was given in a double-blind randomized trial to 796 men with unstable angina or non-Q-wave myocardial infarction in Sweden.[68] The risk ratio of myocardial infarction or death was significantly reduced after one year of therapy to 0.52 ($P<<.01$), as was the rate of severe angina necessitating coronary angioplasty (risk ratio at 1 year = 0.71). There was no increased rate of bleeding. A subgroup analysis was done of patients who continued to have evidence of ST-segment depression but who did not have angina (silent ischemia) following an episode of unstable angina.[69] The aspirin treatment substantially reduced the risk of subsequent myocardial infarction or death over the ensuing year in the group with silent ischemia (4% versus 21%, $P<.01$ at 3 months; 9% versus 28%, $P<.01$ at 12 months).

Alternative Therapies

The Montreal Heart Institute trial of unstable angina (discussed earlier) examined the effect of heparin given at a rate of 1,000 units per hour following a bolus infusion of 5,000 units for six days after hospital admission.[65] Heparin use was highly effective in preventing refractory angina ($P<.01$) as well as myocardial infarction ($P<.01$). When heparin therapy was combined with the use of aspirin, the rate of serious bleeding was slightly increased (3.3% versus 1.7% with heparin alone).

A recent study by Neri Serneri and co-workers examined the effect of treatment with heparin compared with aspirin or recombinant human tissue plasminogen activator in 399 patients with refractory unstable angina.[70] After a bolus of 5,000 units, heparin was infused at a rate of 1,000 units per hour, with the dose adjusted to maintain the partial thromboplastin time 1.5 to 2.0 times baseline. Over the first three days of therapy, the heparin infusion significantly ($P<.01$) decreased the frequency of angina by 84% to 94%, silent ischemia by 71% to 77%, and the overall duration of ischemia by 81% to 86%. The use of bolus heparin alone, aspirin, or recombinant tissue plasminogen activator was not effective. Only minor bleeding occurred.

Recommendations

Patients presenting with acute chest pain may pose a problem in management because the ultimate diagnosis, such as unstable angina or myocardial infarction, may not be immediately clear. As a consequence, recommendations for optimal antithrombotic treatment may be difficult. Some guidelines are suggested, however, based on published clinical trials and current clinical practice:

- In patients with a clear history of unstable angina, immediate therapy with heparin—a 5,000-unit bolus, followed by an infusion of 1,000 units per hour—should be considered. If myocardial infarction does not occur and invasive procedures are not warranted, then aspirin therapy, 325 mg daily, may be started when the use of heparin is discontinued. If refractory unstable angina develops, then heparin therapy can be continued, with laboratory monitoring to maintain the partial thromboplastin time at 1.5 to 2.0 times control.
- If acute myocardial infarction is found, aspirin therapy, 160 mg, can be started along with a consideration of thrombolytic therapy (see earlier discussion). If thrombolytic agents are not used, aspirin therapy may be continued.
- If urgent percutaneous transluminal coronary angioplasty is elected, a regimen of aspirin, 160 to 325 mg daily, can be started before the procedure and continued thereafter (discussed later).
- If urgent coronary artery bypass grafting is indicated, the administration of aspirin should be withheld until the immediate postoperative period (discussed later). If aspirin has been given, however, increased operative bleeding should be anticipated.[71,72]
- In all patients, long-term therapy with aspirin, 325 mg a day, should be considered for secondary prophylaxis of cardiovascular disease.

Chronic Stable Angina

Rationale

In contrast to its role in unstable angina, there is no convincing evidence that platelet-mediated coronary artery thrombosis is responsible for recurrent chest pain in patients with chronic stable angina. Angioscopy has not shown platelet thrombi in these patients.[61] Some studies, however, have suggested that platelets may be activated during or shortly after episodes of angina.[12] Increased urinary excretion of thromboxane metabolites has recently been found in patients with stable angina.[73] The annual mortality for stable exertional angina is approximately 4%, and myocardial infarctions develop in patients with stable exertional angina at a rate of 5% per year.[74]

Major Clinical Trials

Investigators from the Physicians' Health Study analyzed the efficacy of low-dose aspirin therapy in a subgroup of physicians who were previously known to have baseline chronic stable angina but no history of myocardial infarction or transient ischemic attacks.[75] The subjects received 325 mg of aspirin or placebo every other day and were observed for 60 months. The relative risk of myocardial infarction in the aspirin-treated group was significantly reduced to 0.3 ($P<.01$). Their overall cardiovascular risk was reduced by 87% ($P<.01$). There was an increase in the relative risk of stroke of 5.4 ($P<.05$), although none of the strokes were fatal.

In the Swedish Angina Pectoris Aspirin Trial, 2,035 patients (52% male) with chronic stable angina were ran-

domly allocated to taking aspirin, 75 mg daily, or placebo, and outcome events for the ensuing 50 months were then assessed.[76] All patients were given sotalol hydrochloride to control symptoms. The incidence of primary events of subsequent myocardial infarction and sudden death was reduced by 34% in the aspirin group ($P < .01$). The incidence of major hemorrhage was similar in the two groups—aspirin group, 20 patients; placebo group, 13 patients.

Another subgroup analysis of the Physicians' Health Study sought to determine whether administering low-dose aspirin on alternate days could prevent the occurrence of angina pectoris.[77] The relative risk of confirmed new-onset angina in the aspirin group was found to be 1.1. Therefore, this trial found that low-dose aspirin therapy did not reduce the incidence of angina pectoris in previously asymptomatic men.

Recommendations

- Therapy with low doses (325 mg) of aspirin is recommended for men with chronic stable angina for the prevention of myocardial infarction and to reduce the overall cardiovascular risk. A substantially reduced incidence of myocardial infarction, however, must be balanced with a slightly increased risk of nonfatal stroke that was reported in one study.[75]

Coronary Artery-Saphenous Vein Bypass Grafts

Rationale

The postsurgical occlusion of coronary artery-saphenous vein bypass grafts is rather common. During the first month after the operation, approximately 12% of grafts and distal anastomoses will occlude. This complication increases to about 20% at six months. By one year, 41% to 47% of patients will have one or more failed grafts.[12]

During the first month after the operation, vein graft occlusion is most often the result of thrombosis, which is likely to be platelet mediated. In contrast, late occlusion results from intimal proliferation, which may also involve platelets.[78] Studies have suggested that radiolabeled platelet survival was normal in patients whose grafts remained open, whereas platelet survival was shortened in patients whose grafts occluded.[79] Because both early and late occlusion appear platelet mediated, antiplatelet therapy might be effective in maintaining graft patency.

Major Clinical Trials

In 1982 a prospective, randomized, double-blind trial was reported from the Mayo Clinic (Rochester, Minnesota) in which patients undergoing a saphenous vein bypass graft procedure were given dipyridamole, 400 mg a day for two days preoperatively, followed by aspirin, 325 mg daily, beginning seven hours postoperatively by nasogastric tube.[80] Thereafter, patients received 325 mg of aspirin and 75 mg of dipyridamole three times a day. Within a month of the operation, 8% of the patients given the antiplatelet therapy had at least one distal vein graft occluded, whereas grafts were occluded in 20% of patients receiving placebo ($P < .01$). By one year, the incidence of late graft occlusions was significantly reduced from 14% to 9% by the antiplatelet therapy.[81]

The first Veterans Administration Cooperative Study was a prospective, randomized, double-blind study of 772 patients that showed that aspirin given once a day was as effective as aspirin given three times a day in preventing graft occlusion.[82] Neither dipyridamole nor sulfinpyrazone therapy was found to be effective, however. When aspirin therapy was begun 12 hours before the operation, perioperative bleeding was observed, with increased rates of reoperation.[71,72] In this study, the aspirin-treated patients had early graft patency of 94% versus 85% in the placebo group ($P < .05$). After one year, aspirin therapy remained effective, with 23% of grafts occluded in the placebo group compared with 16% in the treated groups ($P < .01$).[83] There was no difference in occlusion rate in vessels greater than 2 mm in diameter. A more recent study from the same group documented that an aspirin regimen started six hours after the operation was equally protective for early graft patency—7 to 10 days—as aspirin administered the night before the operation.[84]

A meta-analysis was done using data from several studies of antiplatelet therapy for coronary artery-saphenous vein graft occlusion performed from 1966 to 1988.[85] It should be noted that all of the studies showed a beneficial effect of antiplatelet therapy, although not all reached statistical significance. The meta-analysis clearly showed that active treatment with antiplatelet therapy was beneficial (overall effect size was 0.3, a significant effect) and that efficacy improved with the early initiation of treatment.

In another Veterans Administration Cooperative Trial, internal mammary artery or saphenous vein grafts to the left anterior descending coronary artery were studied.[86] Patients received either 325 mg of aspirin a day, aspirin three times a day, aspirin plus dipyridamole, 75 mg three times a day, or placebo. The aspirin therapy was started either 6 or 12 hours before the operation. There were no differences in patency rates of either internal mammary artery or saphenous vein grafts with aspirin treatment at one year in these higher flow vessels.

A multicenter, randomized, double-blind, placebo-controlled trial compared a regimen of 50 mg of aspirin given three times a day, 50 mg of aspirin plus 75 mg of dipyridamole three times a day, or placebo in 1,112 patients undergoing a coronary artery-vein graft operation.[87] All patients received 100 mg of dipyridamole four times a day for 48 hours before the operation, with the assigned treatment regimen begun seven hours after the operation. Vein graft angiography was carried out at ten days. The early occlusion rate for distal anastomoses was reduced from 18% in the placebo group to 12.9% in the aspirin-plus-dipyridamole group ($P < .05$).

Recommendations

• Aspirin should be given in a dose of 325 mg a day by nasogastric tube beginning immediately after the operation (within 6 hours). The preoperative administration of aspirin has been associated with excessive bleeding. Although it is not clear that it is beneficial, dipyridamole at a dose of 400 mg per day can be given two days before the procedure but should be discontinued afterwards.

• Aspirin should continue to be administered at that dose for at least three months and probably indefinitely.

• Internal mammary artery or saphenous vein grafts to the left anterior descending artery alone probably do not require antithrombotic therapy. The administration of aspirin may, however, be indicated for underlying coronary artery disease (see recommendations for secondary prevention).

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Monoclonal Antibodies to Endotoxin in the Management of Sepsis

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New monoclonal antibodies directed against the lipid A moiety of the endotoxin present in gram-negative bacteria have been developed to improve the clinical outcome in patients with sepsis. Two studies of monoclonal antibodies HA-1A and E5 retrospectively identified specific patient subgroups showing benefit with therapy. I analyze and summarize the new sepsis nomenclature, the structure of endotoxin, the data implicating endotoxin as a causative agent in septic patients' morbidity and mortality, and specific data from the 2 clinical studies of monoclonal antibody therapy.

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Sepsis remains among the most difficult and frustrating management problems in critical care medicine. Despite aggressive measures using costly technology, the available treatment of patients with sepsis still results in an unacceptably high mortality. With the development of antiendotoxin monoclonal antibodies, the question for physicians is whether these new therapies will change the morbidity or mortality of this disorder.* Two new monoclonal antibodies have been produced against the lipid A moiety of the endotoxin component of gram-negative bacterial cell walls, in the hope that blocking lipid A would prevent the manifestations of sepsis. Recent controlled trials using the HA-1A (Centocor, Inc, Malvern, Pennsylvania) and E5 (Xoma Corporation, Berkeley, California) monoclonal antibodies in septic patients have identified subgroups of the study populations who had statistically significant decreases in mortality and improvement in the recovery of organ dysfunction after early administration of these monoclonal antibodies versus placebo. The characteristics of the subgroups benefiting from treatment in the two studies differ, however, and important questions remain as to which product is useful in these patients or whether either drug is of enough benefit to warrant its high cost.

I will review the following concepts:

- The proposed sepsis nomenclature to classify patients who have sepsis or the sepsis syndrome,
- The structure of endotoxin and the manipulations of its biochemical milieu that allow the development of monoclonal antibodies to the lipid A component of endotoxin,
- The experimental observations regarding endotoxin infusion into animals and humans,
- The correlation between the serum detection of endotoxin and blood cultures positive for gram-negative bacteria in septic patients, and
- The discrepancies between two clinical trials using monoclonal antibodies directed against lipid A.

*See also "Therapies Directed Against Endotoxin—Has the Time Come?" by Z. M. N. Quezado, MD, and W. D. Hoffman, MD, on pages 424-425 of this issue.

Definition of Sepsis

Many clinicians use the term "sepsis" to refer to patients who have evidence of infection and hemodynamic instability. Until recently, no attempts had been made to standardize the various terms used interchangeably, including bacteremia, septicemia, sepsis, and septic shock. In 1989 Bone and co-workers proposed a new set of broad definitions that described sepsis more completely. Specifically, bacteremia defines blood cultures positive for bacterial pathogens; sepsis refers to a condition of high suspicion or an obvious source of infection, accompanied by fever or hypothermia, tachypnea, and tachycardia; the sepsis syndrome requires evidence of altered organ perfusion—metabolic acidosis, elevated lactate levels, renal failure with oliguria, hypoxemia, and altered mental state—in addition to sepsis, but does not require positive blood cultures; and, finally, septic shock refers to patients with the added complication of hypotension and can be further classified as refractory if it persists for more than an hour despite fluids and pressor support.[1]

Gram-negative Bacteria and Endotoxin

The clinical progression of infection that leads to hemodynamic collapse and death has been described as the sepsis cascade.[2] A source of infection such as pneumonia or abscess may result in the release of bacterial toxins into the bloodstream. These toxins may be either bacterial products such as staphylococcal enterotoxin or components of the cell walls, including endotoxin. These toxins can enter the bloodstream and interact with the cells of

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ABBREVIATIONS USED IN TEXT

Ig = immunoglobulin
LPS = lipopolysaccharide

the immune system, causing the release of endogenous mediators such as interleukins and tumor necrosis factor. The interaction of all these mediators causes cardiovascular insufficiency as a result of a depressed left ventricular ejection fraction, left ventricular dilatation, and increased permeability of the vascular endothelium. Hypotension and decreased end-organ perfusion may result, possibly leading to death.

Gram-negative bacteria account for a substantial proportion of the infections that cause this sepsis pathophysiology, but other infectious agents initiate the same sequence of events that may lead to shock and death. Both gram-positive and gram-negative bacteria produce the same pattern of cardiovascular changes associated with sepsis in dogs.[3] The essential difference between gram-positive and gram-negative bacteria lies in the structure of their cell walls; endotoxin is absent from the cell wall of gram-positive bacteria, which comprises mainly peptidoglycans and techoic acids. Endotoxin has been shown not to be the universal mediator of septic shock, as dogs infected with gram-positive bacteria did not have evidence of endotoxin but showed the same cardiovascular changes as in gram-negative sepsis. It is important to remember that the presence of endotoxin is sufficient but not necessary to cause sepsis.[3] Many investigators continue to search for the final common mediator in the pathway of injury leading to sepsis.

Endotoxin, a lipopolysaccharide found in the outer membrane of gram-negative bacteria, consists of three main regions. The highly variable oligosaccharide, or "O region," conveys antigenic specificity to different types of gram-negative bacteria and can activate the alternate pathway of complement. The R-core region is less variable among different gram-negative bacteria; therefore, antibodies to this region can be cross-protective against infection caused by different gram-negative bacteria. The lipid A component of the cell wall is the most highly conserved region and is considered the toxic element of endotoxin; it can stimulate the release of tumor necrosis factor and can directly activate the classical pathway of complement activation.[4] The new monoclonal antibodies are thought to bind to lipid A, thereby blocking its activity.[5]

Experimental infusion of endotoxin into animals and humans produces the same systemic responses and cardiovascular changes associated with sepsis, supporting its role as a mediator in sepsis. In animals, endotoxin infusion causes fever, the release of interleukin-1 and tumor necrosis factor, complement activation, disseminated intravascular coagulation, and shock.[4] In humans, after a 45- to 60-minute quiescent period, the infusion of endotoxin may cause an acute-phase response with fever, arthralgias, myalgias, headache, and nausea; this occurs within two to three hours of infusion and usually subsides by five to eight hours. Administering endotoxin also results in a hyperdynamic cardiovascular state with a depressed and dilated left ventricle and reversible abnormalities of ventricular performance and volume. In addition, the infusion of endotoxin causes alterations in pulmonary function and gas exchange and activates the fibrinolytic system.[6]

Evidence exists against an important role for endotoxin in sepsis. Mice have different sensitivities to endotoxin, varying by as much as 5,000-fold, yet all have a similar lethal response when infused with live gram-negative bacteria.[7] Human volunteers can be vaccinated against endotoxin, but when given typhoid or tularemia, they were not protected clinically from these illnesses.[8] Finally, the measurements of endotoxin in the serum of patients who have gram-negative sepsis have not consistently correlated with the clinical manifestations or outcomes.[9]

Endotoxemia and Positive Blood Cultures

The rationale for therapy with the new monoclonal antibodies to endotoxin assumes the presence of endotoxin in the serum of all patients with gram-negative sepsis. Recently the chromogenic limulus lysate assay was used to detect serum endotoxin, based on the ability of endotoxin to activate a proenzyme that cleaves a *p*-nitroaniline group from the chromogenic substrate.[10] Investigators studied 110 patients with shock; 100 had shock resulting from infection, and 10 had nonseptic causes of shock. Only 43 of the 100 septic patients had endotoxin in their serum; the assay was positive in 20 patients on the first serum specimen, and in the other 23 patients it became positive within the first 20 hours after study entry. Most of the 43 patients had multiple serum specimens positive for endotoxin, and in all patients who recovered, the endotoxin had cleared from their bloodstream. Endotoxin was uncommon in patients with nonseptic causes of shock, such as cardiac failure; only 1 of 10 patients with nonseptic shock had detectable endotoxemia. In addition, the presence of endotoxin in the 43 septic patients was significantly associated with blood cultures positive for bacteria, lactic acidemia, decreased systemic vascular resistance, and depressed left ventricular function—all features consistent with a clinical diagnosis of sepsis.

Subgroup analysis of the patients who had both endotoxin detected in their serum and positive blood cultures revealed that only 26% of patients with positive blood cultures had gram-negative bacteria—that is, gram-negative bacteremia never developed in 74% of patients with endotoxemia. This suggested that endotoxin may be present when the patient does not have gram-negative bacteremia. Conversely, 14% of patients without endotoxin had gram-negative organisms grown from their blood, implying that endotoxin may be rapidly cleared from the bloodstream. Further, endotoxin was detected in the serum of 12 of 18 patients who had blood cultures positive for gram-positive bacteria and fungi, suggesting that there may have been undetected coincident gram-

negative infection or that endotoxin leaked from another focus of infection. Overall, the subgroup of patients with both endotoxin detected in their serum and blood cultures positive for all pathogens had a substantial increase in the occurrence of renal failure, the adult respiratory distress syndrome, and death.

The results of this study demonstrate an inconclusive relationship between endotoxemia and the isolation of gram-negative bacterium in the blood of patients with sepsis. Most patients with septic shock did not have detectable endotoxin in their blood; this may result from infection with pathogens other than gram-negative bacteria, the rapid clearance of endotoxin, or local sequestration of the endotoxin. Most patients with endotoxemia never had cultures positive for gram-negative bacteria, suggesting that endotoxin can persist even after the clearance of bacteria from the blood or that there may be other sources of endotoxin leaking into the circulation. These studies confirm that the presence of endotoxin is sufficient but may not always be a part of the pathogenesis of sepsis.[10]

Monoclonal Antibodies to Endotoxin

Antibody to intact endotoxin, the complete lipopolysaccharide (LPS) portion of the gram-negative outer membrane, is directed primarily against the highly variable O-region side chains, which differ greatly between different strains of gram-negative bacteria; such an antibody would protect against the effects of LPS from one bacterial strain but would be much less effective against LPS from other bacterial strains. Antibodies to the lipid A moiety, however, the most highly conserved region of LPS among various gram-negative bacteria, should be protective against all gram-negative organisms.

Investigators circumvented the problem of antigenic diversity of the gram-negative bacteria by using a gram-negative bacterium containing only the core and lipid A elements, devoid of the variable side chains.[11] The J5 mutant of *Escherichia coli*, 0111:B_4, lacks the enzyme uridine 5′-diphosphate-galactose 4-epimerase and cannot incorporate the exogenous galactose into LPS; this epimerase deficiency prevents the attachment of side chains. The J5 mutant contains only the core determinants of LPS, including lipid A, *N*-acetylglucosamine, 2-keto-3-deoxyoctonate, heptose, and glucose.[11]

In rabbits immunized with the J5 mutant, high levels of antibody to J5 LPS developed; they were protected against a Shwartzman reaction using purified endotoxins from other bacteria including *E coli*, *Salmonella typhimurium*, and *Neisseria meningitidis*. Neutropenic rabbits treated with J5 rabbit antiserum had increased survival compared with controls when given gram-negative infections. In contrast, antiserum to the intact LPS of the parent *E coli* strain, in which the core elements are concealed by the O side chains, did not confer protection against infection by other bacteria; J5 antiserum adsorbed by J5 LPS was also ineffective, but antiserum to purified lipid A-rich J5 LPS was fully cross-protective.[11]

In 1982 human J5 antiserum was prepared by vaccinating healthy men with heat-killed *E coli* J5.[11] In a randomized, controlled trial, it was found that human antiserum to J5 resulted in a statistically significant decrease in mortality in patients with bacteremia and shock.[11] In 1985 the human J5 antiserum was given prophylactically to surgical patients; while it had no effect on the incidence of gram-negative infections, there was a statistically significant reduction in both the incidence of shock and the mortality in patients with shock, especially in the group requiring abdominal operations.[12]

Although antiserum against the modified LPS of the *E coli* J5 mutant showed clinically significant reductions in morbidity and mortality in rabbits and humans, the specific type of antibody conferring benefit was still unknown. In 1988 an IgG-purified antibody from pooled plasma obtained from volunteers immunized with the *E coli* J5 mutant was used in a double-blind, randomized study of patients with gram-negative infections.[13] There was no difference in mortality between the patients given the *E coli* J5 immunoglobulin (Ig) G antibody versus controls given standard IgG antibody. It was concluded that IgG antibody was not responsible for the protective benefits of the antiserum.[13] Finally, in the same year with the use of another type of mutant LPS from *Salmonella minnesota*, it was reported that the protective activity of the antiserum resided in the IgM antibody and that the IgG antibody did not bestow protection.[14] The subsequent development of the monoclonal antibody to the *E coli* J5 mutant LPS has obviated the need for the difficult and costly establishment of a reproducible supply of human antiserum and has avoided the risks of disease transmission from the parenteral use of human blood products.

The evaluations of the two monoclonal antibodies to the endotoxin component of the *E coli* J5 mutant have now been reported. The HA-1A monoclonal antibody developed by Centocor and the E5 monoclonal antibody developed by Xoma were studied in prospective, multicenter, randomized, double-blind placebo-controlled trials. They both used clinical features similar to those of the "sepsis syndrome" definition as the inclusion criteria: evidence of clinical infection with changes in vital signs and altered end-organ perfusion.[5,15] In both studies, patients were observed for 28 days or until death.

Both agents are IgM antibodies, but the HA-1A is a human product and E5 is a murine product. The antibodies HA-1A and E5 both act against the lipid A moiety of a wide variety of gram-negative bacterial endotoxins. The administration of HA-1A to study patients included a single 100-mg dose of the drug given within a mean time period of 14 hours after study entry; E5 was given in two doses, the first dose of 2 mg per kg within 8 hours of meeting the entry criteria, followed by the second dose 24 hours later.

The determination of drug efficacy depended on the specific identification of subgroups defined differently in the two studies. In the first, positive blood cultures were used to define "bacteremia," and the second used the term "sepsis" to refer to a positive culture from speci-

mens of blood or a body fluid.[5,15] Both studies evaluated the drugs' effects on mortality and on the resolution of organ failure.

The results from the HA-1A study demonstrating drug efficacy are based only on the subgroup of 200 patients who had blood cultures positive for gram-negative bacteria, or 37% of the 543 patients in the entire study group. The antibody HA-1A was given to 262 patients, and 281 patients received placebo. The sources of infection were primarily in the genitourinary and gastrointestinal tracts, and the most common pathogens included *E coli* and *Klebsiella, Enterobacter,* and *Pseudomonas* species. In the subgroup of patients with bacteremia, there was a notable decrease in mortality in patients treated with HA-1A; 32 of 105 patients died (30%) compared with 45 of 92 control patients who died (49%), for an overall reduction in mortality of 39% ($P = .014$). Further subdividing the group of patients with bacteremia into two subgroups with and without shock showed a statistically significant decrease in mortality in both groups. In the group with shock, death occurred in 18 of 45 patients (33%) treated with HA-1A compared with 27 of 47 control patients (57%), for an overall 42% reduction in mortality ($P = .017$). In the group without shock, 14 of 51 patients (27%) treated with HA-1A died compared with 18 of 45 control patients (40%), an overall reduction of 33% (Table 1).

TABLE 1.—*Reduction in Sepsis Mortality Using Monoclonal Antibodies to Endotoxin*

Patient Population	*Mortality, No. Patients Died / No. Infected (%)*		
HA-1A study: Subgroup with bacteremia (n = 200)*			
	Overall	*Without Shock*	*With Shock*
Placebo	45/92 (49)	18/45 (40)	27/47 (57)
HA-1A	32/105 (30)	14/51 (27)	18/45 (33)
E5 study: Subgroup with sepsis (n = 316)†			
	Overall	*Without Shock*	*With Shock*
Placebo	62/152 (41)	27/63 (43)	36/89 (40)
E5	62/164 (38)	22/74 (30)	41/90 (45)

*The HA-1A (Centocor, Inc, Malvern, Pa) study showed efficacy only in the subgroup of patients identified retrospectively with gram-negative bacteremia, defined as positive blood cultures. A statistically significant reduction in mortality occurred in all patients of the subgroup, in both those with and without shock ($P < .05$).

†The E5 (Xoma Corp, Berkeley, Calif) study showed efficacy only in the subgroup of patients identified retrospectively with gram-negative sepsis, defined as gram-negative bacteria detected in cultures of either blood or body fluid. A statistically significant reduction in mortality occurred only in the patients without shock ($P = .01$); there was no reduction in mortality in the subgroup overall or in the subgroup with shock.

Substantial organ-system failure—manifested by shock, disseminated intravascular coagulation, acute renal failure, acute hepatic failure, or the adult respiratory distress syndrome—occurred in 123 of the 200 patients with gram-negative bacteremia. During the first seven days after treatment, the complicating conditions resolved in 26 of 62 patients given placebo (42%), compared with 38 of 61 patients given HA-1A (62%) ($P = .024$), showing a significantly greater resolution of organ failure.

There was no protection by HA-1A in patients with focal nonbacteremic gram-negative infection and in the patients without any evidence of gram-negative bacterial infection. In the entire study group of 543 patients, there was no statistically significant reduction in mortality overall. In summary, HA-1A therapy reduced mortality only in the subgroup of study patients who had blood cultures positive for gram-negative bacteria, whether the patients were normotensive or in shock. The drug also enhanced the resolution of organ-system dysfunction in this same subgroup of patients with gram-negative bacteremia.[5]

The initial E5 study enrolled 486 patients with a systemic response to infection suspicious for a gram-negative bacterial cause,[15] but analysis of the data focused on the 316 patients with gram-negative sepsis defined as a positive blood or body fluid culture. In the group of patients with gram-negative sepsis, there was no overall reduction in mortality. In the subgroup of patients with sepsis and shock, the E5 antibody also did not reduce mortality. The E5 antibody showed a statistically significant reduction in mortality only in the subgroup of patients with sepsis who were normotensive; death occurred in 43% of control patients compared with 30% of patients treated with E5 ($P = .01$). Of note, the benefit of E5 in this subgroup of patients without shock occurred regardless of whether the qualifying culture with a gram-negative bacillus was from blood or another body fluid (see Table 1).[15]

The preliminary analysis, however, of a second trial of E5 in 847 patients, performed to test the hypothesis that E5 benefits patients who had gram-negative sepsis but were not in shock, did not show improved survival in the 530 patients with documented gram-negative sepsis.[16] A trend toward improved survival was seen in a subgroup of 139 treated patients who had major-organ failure without refractory shock.

A reduction in organ failure also resulted from therapy with E5 in the first study, but again only in the same subgroup of patients with gram-negative sepsis who were normotensive; 19 of 35 (45%) patients treated with E5 had improved organ function, but only 8 of 27 (30%) of control patients had improvement ($P = .05$).[15] There was no reduction in organ failure in patients with sepsis and shock. In summary, administering E5 reduced mortality in the subgroup of study patients who had positive cultures of blood or body fluid, but only if they were not in shock. The drug did resolve organ system dysfunction, but again in the subgroup of patients with sepsis who were not in shock.

Both drugs had rare reported side effects of hives, flushing, rash, and transient hypotension. Patients treated with HA-1A reportedly did not have the development of antibodies to the HA-1A drug, whereas anti-mouse antibodies to the murine drug did develop in 47% of patients treated with E5.

Discussion

Therapy directed against the endotoxin component of the gram-negative bacterial cell wall is based on evidence that the infusion of endotoxin into animals and humans

results in clinical manifestations and hemodynamic changes similar to those that occur in sepsis. Because it is known that other infectious agents such as gram-positive bacteria may cause the same pathophysiology, endotoxin is a sufficient but not a necessary factor to cause sepsis. The presumed universal mediator of the final common pathway of sepsis remains elusive.[3]

Preliminary studies with antiserum to endotoxin from the *E coli* J5 mutant in animals and humans led to the elaboration of specific monoclonal antibodies of the IgM class directed against the lipid A moiety of LPS for use in clinical trials of patients with evidence of gram-negative bacterial infection. Monoclonal antibodies to endotoxin prevent sepsis by blocking the interaction of the toxic lipid A moiety with the body's cellular defenses.

Understanding the implications of the studies by Ziegler and Greenman and colleagues using two monoclonal antibodies requires a familiarity with the definitions of the patient subgroups in these studies. Ziegler and co-workers used the term bacteremia to identify those patients who had blood cultures positive for gram-negative bacteria; Greenman and associates used the term sepsis to refer to those patients who had positive blood cultures or positive body fluid cultures. Although bacteremia is a stricter definition requiring the detection of the pathogen in the blood and thus implying the simultaneous presence of endotoxin in the serum, the broader term sepsis as used by Greenman and colleagues includes the possibility that endotoxin may be present in the blood as the result of a leak from a focal site of infection, without confirmation of bacteria in the blood. Of note, the entry criteria for both studies are similar to the definition of the sepsis syndrome proposed by Bone, which does not require that there be blood cultures positive for bacteria.

Retrospective analysis of both trials suggests that therapy, initiated at study entry before final culture results, only benefits patients with gram-negative bacterial infection and cultures of blood or body fluids positive for such. Unfortunately, most clinicians are too familiar with the need for aggressive empiric therapy for all patients with deteriorating clinical conditions consistent with sepsis, usually before culture results can be obtained. Thus, a prospective selection of candidates for these therapies will be difficult because no clinical features predict the subsequent development of bacteremia.[17,18]

Both studies showed drug efficacy in patients who had positive cultures by reduced mortality and by the association with resolving organ failure. The two studies using similar products had two different results, however. Administering HA-1A benefited all patients with gram-negative bacteremia who were treated with the drug, regardless of the presence of shock. Giving E5 benefited patients with cultures positive for gram-negative bacteria only if they did not have shock in the initial study; even this result was not confirmed in a follow-up study using E5. The reasons for these different results are not explained by the manufacturers of either drug. Therefore, the data from these studies are inadequate to lead to a reasonable clinical decision as to which drug to use.

Ongoing analyses of the data from the HA-1A study and the two E5 studies question the conclusions of efficacy in the subgroups who appeared to benefit from therapy.[19] A detailed independent analysis of the second E5 study may clarify the results that failed to confirm the drug efficacy found in the first study. Critics who challenge the efficacy of using HA-1A in patients with gram-negative bacteremia suggest that administering HA-1A may, in fact, benefit only patients with gram-negative bacteremia who are in shock. Other concerns about the HA-1A study focus on the following:

- The number of patients receiving inadequate antimicrobial therapy in the placebo group is disproportionate,
- Raw APACHE II scores were used instead of individual risks,
- The differences in the time of administering HA-1A or placebo possibly influenced outcome;
- The antibody HA-1A had its effect primarily in patients at study centers with high case-fatality rates for gram-negative bacteremia, and
- The HA-1A group had a higher mortality compared with the placebo group in patients who had nonbacteremic gram-negative infections.[19]

Ziegler refutes these criticisms, noting that licensure has been unanimously recommended by a United States Food and Drug Administration advisory panel, and rejects the suggestion that additional placebo-controlled trials to demonstrate efficacy are warranted.[20]

Finally, the data from the study by Danner and co-workers shed doubt on the correlation between blood cultures that are positive for gram-negative bacteria and the presence of endotoxin in the serum.[10] Neither monoclonal antibody study reported the measurement of serum endotoxin levels. The data from this study did not show a correlation between an early detection of endotoxin and a later development of gram-negative bacteremia. As previously noted, only 26% of patients with detectable endotoxemia had blood cultures positive for gram-negative bacteria—that is, most never had a positive blood culture. In addition, 14% of the patients without endotoxemia had cultures positive for gram-negative bacteria, implying that endotoxin may be rapidly cleared from the bloodstream. Overall, most of the patients with sepsis in this study never had detectable levels of endotoxin. Either endotoxin from gram-negative bacterial infection exists only transiently in the blood or other mediators may be more important in the initiation of the sepsis cascade.[10] Therefore, the detection of endotoxin cannot be used in the process of deciding whether to use these drugs.

Other investigators have voiced concerns about the safety of the monoclonal antibodies.[21,22] A trend toward increased mortality was noted among patients without gram-negative bacteria in the treatment group, raising the possibility that HA-1A may have unrecognized toxic-

ity.[21] The potential for the development of human antibodies against the foreign antibodies has also been addressed.[15,22] The antibody E5 is a murine product developed by the fusion of murine splenocytes immunized against the J5 mutant of *E coli* with murine myeloma cells; HA-1A is the product of the fusion of human spleen cells and a mouse-human heteromyeloma.[22] None of the 116 patients treated with HA-1A in the series reported by Ziegler and co-workers had detectable levels of anti–HA-1A antibodies using a double-antigen radiometric assay with a sensitivity of 3.5 μg of antibody per milliliter of serum.[5] In the study by Greenman and associates, anti-murine antibodies appeared late in 86 of 182 patients (47%) treated with E5; a standard enzyme immunoassay with a sensitivity of less than 1 ng per ml was used to detect antibodies, and the researchers defined a response as occurring when a fourfold increase over baseline titer was detected.[15] The failure of the Ziegler group to detect anti–HA-1A antibodies may have resulted from limited sampling and the use of a less sensitive assay, since none of the patients' antibody responses to E5 were as high as 3.5 μg per ml, the threshold for detection in Ziegler's assay.[15] The possibility of antibodies developing to either monoclonal antibody has as-yet-unknown implications for the subsequent administration of the drug or for the use of other murine products.

Finally, some authors have anticipated the magnitude of the additional costs of introducing an expensive new therapy into the arsenal of critical care medicine. An additional expenditure of $1.6 billion has been estimated for HA-1A based on the current incidence of gram-negative bacteremia, the percentage of Ziegler and co-workers' patients with gram-negative bacteremia, and a conservative cost estimate of $2,000 per patient.[17]

A sophisticated economic assessment was made of the use of HA-1A based on the results of the study by Ziegler and colleagues.[23] Issues of concern to clinicians were addressed by a cost-effectiveness analysis based on the following:

- A cost of $3,750 per dose was based on a recently established price for HA-1A in the Netherlands;
- The HA-1A therapy might affect acute-care hospital costs, resulting in a calculated incremental cost of $19,200 for the care of each additional survivor benefiting from HA-1A therapy (excluding the drug cost);
- Adjusted life expectancies were incorporated to reflect comorbid conditions in patients with sepsis, yielding an average gain of five years of life per survivor; and
- Two treatment models were used to illustrate the effects of liberal or strict criteria for administering the drug; the first model assumes treatment with HA-1A for all patients with sepsis, and in the second model patients receive HA-1A only if they have positive results from a hypothetical test that can determine the presence of endotoxemia or gram-negative bacteremia before therapy is instituted.

It was concluded that HA-1A therapy alone might cost $1.5 billion annually, resulting in an overall increase of $2.3 billion to national health care costs. Cost-effectiveness ratios reveal a cost of $24,100 per year of life gained if all patients with sepsis are treated; this compares favorably to the use of colestipol hydrochloride as a cholesterol-lowering therapy at $91,280 in 1991 dollars and to the use of zidovudine in asymptomatic patients with the human immunodeficiency virus at a range of $6,553 to $70,526. If a test (estimated at $100 in the model) could identify all patients with endotoxemia or gram-negative bacteremia before therapy is started (thus limiting the use of the agent), then potentially the cost per year of life saved could be reduced from $24,100 to $14,900, with an overall savings of $1 billion.[23] It appears that factors such as drug cost, the influence of comorbid conditions on survival benefits, and the variability of hospital costs all directly affect the possible cost of HA-1A therapy in sepsis; but the analysis suggests that a restricted use of HA-1A in a prospectively identified group of patients with gram-negative sepsis has the greatest potential for containing health care costs.

In conclusion, therapy for sepsis with monoclonal antibodies directed against the lipid A moiety of endotoxin of gram-negative bacteria has been shown to have limited efficacy in a subgroup of patients identified retrospectively. The discrepancy between the studies of HA-1A and E5 remains unanswered. More investigation is required before these drugs can be used in all patients suspected of having gram-negative sepsis.

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* * *

LETTER FROM HOME

If I had a butler
I'd call him Contumely
and yet forgive him
the tray of toast he brings
dry as these bones I inhabit.
My body's insults bruise my tea,
here and now under the apple
and the pear.
Then I had such a long fall
yesterday, half the length
of the stairs, and now
the outrageous spring.
What little I've had of butlers
left years ago before
the liver spots.
They *say* it's spring again.
It must be. I hear the tink
tink, tink of nutbirds.
I am delighted the trillium
you sent me before the fall
survived the winter.
My keeper is scornful.
Small and insignificant
she says, but doesn't know
the miracle of survival,
tight in my mind.
The enclosed check is for your
daughter's daughter—please forward.
May I have a new address soon?
I send much love. Trillium.

THOMAS C. BUELL©
Portland, Oregon

Epitomes

Important Advances in Clinical Medicine

Plastic Surgery

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in plastic surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in plastic surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Plastic Surgery of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, PO Box 7690, San Francisco, CA 94120-7690

Face-lift and Blepharoplasty

SUBSTANTIAL IMPROVEMENTS in the postoperative results of face-lift procedures have been made over the past five years. This is primarily because of advances in the understanding of facial anatomy and the application of craniofacial surgical techniques. Problems of the lower face, including jowling and redundant neck skin, fat, and muscle, have been virtually eliminated with extensive subcutaneous undermining, platysmal plication or resection, superficial musculoaponeurotic system operation, and the direct or indirect removal of abnormal fat deposits of aging. Many problems of the upper face have also been eliminated with various techniques of brow lifting through a coronal or forehead hairline incision. Levels of brow-lift dissection have been successful at the subcutaneous, supragaleal, or subgaleal planes with varying amounts of forehead muscle resection to eliminate vertical frown lines at the root of the nose and transverse forehead lines above the eyebrows. Superior repositioning of the eyebrows not only corrects the descent that occurs with aging, but also gives a dramatic improvement to the hooding and redundancy of upper eyelid skin that was ineffectively and inappropriately treated with blepharoplasty in the past. The remaining challenge is to rejuvenate the central third of the face, including the nasolabial folds and malar pouches that descend with age.

One approach to the middle third of the face has been to dissect at the subperiosteal level, freeing all tissues from the zygoma, zygomatic arches, maxilla, and nose. In this subperiosteal face-lift, after these areas are widely undermined and fascia detached from their insertions, the deep structures are repositioned superiorly, suturing midfacial soft tissues to the temporalis fascia. While this technique appears to improve the midcheek and malar regions, there is little nasolabial fold improvement. This type of "craniofacial face-lift" is also an extensive procedure and can have the complication of paresis of the frontal branch of the facial nerve. Another approach is to extend the dissection from the face-lift anteriorly to the nasolabial fold and defat the fold directly. Possible complications, including devascularization of the face-lift flap, hematomas, and nerve damage, do not appear to be substantial. Another similar procedure takes the platysma muscle, the cheek fat of the midface, and the orbicularis muscle as a single composite flap and elevates it out to the nasolabial fold with less emphasis on removing nasolabial fat. This technique has been used since 1990 with good results and no orbicularis oculi motor dysfunction. Other techniques to address the nasolabial fold have included liposuction, fat curettage under direct visualization, and resection of the levator labii superioris alaeque nasi muscle. Continued evaluation of all of these techniques, used with the proper indications, should overcome the final barriers to complete facial rejuvenation.

A precise diagnosis of eyelid deformities is critical to obtain superior results with the many approaches now available for eyelid restoration. Upper blepharoplasty analysis involves examining the forehead for possible descent, the eyebrow and upper orbital region soft tissues, the eyelid skin, orbicularis muscle redundancy, and periorbital fat. Removing heaviness and bulkiness in the lateral upper orbital region may involve resecting fat behind the orbicularis oculi superficial to the usual retroseptal areas of fat resection. Bony contouring of the orbital rim may also be appropriate with craniofacial techniques. Access to the medial orbital fat compartment through a coronal incision during a brow lift, without any external incision on the eyelid, has been recently described. Lower blepharoplasty without incisions, known as transconjunctival lower lid blepharoplasty, is also gaining popularity. Although originally indicated for younger patients with isolated fat prominence and little skin redundancy, it is increasingly found to give good results in

older patients with moderate perceived skin excess. Only fat is resected through a division of the conjunctiva and capsulopalpebral fascia of the everted lower lid; however, it appears that the change in contour of the skin of the lower lid uses up the apparent excess. The result is a smooth lower eyelid without bagging. Although transconjunctival blepharoplasty has gained in popularity in the past several years and is thought by some to prevent the occurrence of lower eyelid ectropion, reports are starting to surface of complications including ectropion, entropion, and diplopia. Some surgeons are starting to combine transconjunctival blepharoplasty with a chemical peel of the eyelid skin to correct fine wrinkling. For a lax lower eyelid that may be prone to retraction postoperatively, numerous procedures to fix the lateral canthus or lateral tarsal border of the lower eyelid to the lateral orbit have substantially improved surgical results. Tarsal suspension or fixation procedures are also gaining acceptance to improve results in lower eyelids with normal tone. No evidence currently exists to support a benefit of laser blepharoplasty over conventional techniques.

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Coverage of Burn Wounds

CLOSURE OF THERMALLY injured wound beds remains the main challenge of a pediatric burn team because a patient's survival depends on successful wound closure using viable, permanent skin. Burns of as much as 40% of the total body surface area can be easily covered with sheet or meshed autografts in a set of serial excisions and grafting procedures. Injuries covering as much as 70% of the total body surface area usually require the addition of a temporary skin coverage material while waiting for donor sites to repopulate or for deep dermal areas to epithelize. Traditionally these temporary materials have included porcine xenograft, cadaveric allograft, and biosynthetic material, each of which has various disadvantages, such as expense, short shelf life, and viral disease transmission.

Closing the extensive wounds of patients with burns of greater than 70% of their total body surface area is problematic. It now appears that the use of cultured skin grafts is feasible for the timely closure of wounds in patients with massive burns.

When a patient is admitted to the burn unit, a sterile skin biopsy is taken from an unburned area of skin and transported to a skin bank. Many burn centers are affiliated with a local skin bank, and others use commercial companies to grow skin. The skin is then processed by a variety of tissue culture techniques until the desired quantity of skin is grown in culture flasks. As much as a 10,000-fold increase in skin can be grown from a single 2-cm^2 biopsy specimen over about three weeks. During this time the patient undergoes serial debridements and, where possible, coverage of the wound with repeated harvesting of available autogenous tissue. Cadaveric or synthetic skin is then used to cover the remaining areas until the cultured skin is ready.

When the patient is stable and the wound bed is noninfected, the cultured skin is transferred to the patient and placed on the wound bed in a manner similar to autograft placement. Postoperative nursing care is slightly more intensive, requiring the patient to be kept sedated, and may even delay a return to normal rehabilitation activities. The rate of "take" of the skin grafts in part varies with the familiarity of the surgical and nursing staff with the technique but is reported to be nearly 80% under ideal conditions.

Unfortunately, there are still many problems associated with this grafting technique. When the cultured cells consist of only epidermis, the graft is thin and fragile. If it is not placed onto a dermal bed, it has not been shown to form rete pegs, anchoring fibrils, or a basement membrane, and patients have problems with increased fragility, blister formation, and shear. This has necessitated repeated grafting with either more cultured skin or autologous tissue. The cultured skin seems to be hardier when it is placed onto a dermal bed, either an unexcised dermal wound base or an allograft dermal base that has been previously placed on the wound bed and allowed to vascularize.

Substantial cost is associated with this technique (between $1,000 and $9,000 per each percentage of body surface area covered), and the length of hospital stay is increased. Long-term results with scarring are still undergoing evaluation. Research on this technique is ongoing, and cultured skin grafting will eventually become routine as another method for achieving timely wound closure for patients with massive burns.

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Wrist Pain

WRIST PAIN is a challenging diagnostic dilemma. Most patients with wrist pain come to a hand surgeon after a series of failed conservative measures and a battery of unrevealing studies.

As with any evaluation, the history is the single most important feature. If obvious injury is excluded, then careful questioning must include the patient's occupation and any daily repetitive tasks. While the wrist may be the focus, the entire upper extremity from the neck to the fingertips must be included in the examination. Even the most trivial and seemingly unrelated activity may give important clues to the nature of the problem. For this reason, several visits to the physician may be necessary.

Several large categories can be excluded by the physical examination. The key is to determine whether the disorder is in the soft tissues or the bony and ligamentous elements. The patient will often refer to a deeper pain when describing maladies of the latter; soft tissue problems are usually palpable. At several points in the examination, it is useful to refer to the uninvolved side when making judgments about range of motion, color, perfusion, position, swelling, and strength.

A few key tricks to localize pain are helpful. Palpation of each wrist bone is mandatory. Grinding the metacarpals and the radius and ulna against the carpals and noting pain or grinding sensations can give clues to degenerative changes. Also, any excessive laxity or instability with crepitus when going through full ranges of motion (compared with the uninvolved side) can give clues to ligamentous tears or disruptions. In addition, it is important to stress each extensor compartment to rule out tendinitis. On the flexor aspect, tests for Phalen's and Tinel's signs should be done to rule out carpal tunnel syndrome.

Confirmatory roentgenograms are the next step in management. They must include all four views—lateral, semipronated oblique, posteroanterior, and scaphoid—including comparative views of the uninvolved side. Accurate communication between the radiologist and the physician must be maintained to avoid overinterpreting the results. In addition, the investigator must critically review the x-ray film because even simple supination and pronation of the forearm will change spatial relationships in all of the articulating surfaces of the carpal bones.

Nerve conduction studies can give clues to compression syndromes masquerading as wrist ailments and should be done early to exclude nerve compression before expensive and lengthy radiologic scans are undertaken.

The next tier of testing frequently begins with bone scanning. Fractures may be evident by increased uptake after only 48 hours. A normal scan, especially if taken a week after injury, should show that a bony injury is absent. Scans can give clues to local or diffuse degenerative disease. If they also reveal ligamentous injury, arthrography or arthroscopy should be done. Computed tomography and magnetic resonance imaging are the next level of study. Magnetic resonance imaging is most useful in diagnosing marrow abnormalities such as avascular necrosis of the lunate, and computed tomography is useful to detect soft tissue and bony masses.

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Cleft Lip and Palate and Craniofacial Operation

THE SURGICAL CORRECTION OF craniofacial deformities has advanced swiftly over the past few decades. The goal remains constant: rehabilitate these patients to a normal appearance.

The pioneering efforts of Paul Tessier of Paris brought the field of craniofacial surgery to the forefront of plastic surgery. His techniques included intracranial access to the orbit and extensive subperiosteal dissection of the soft tissue with wide exposure of the underlying bony structures. This permits direct visualization for extensive bone grafting to either fill or augment the facial skeleton.

Plastic surgeons see numerous facial and skeletal deformities that can be divided into two categories: those associated with a clefting phenomenon and those related to a premature closure of the calvarial sutures. Within the latter group, the skull is unable to conform to the developing brain, leading to compensatory growth and abnormal cranial configurations. These patients may have a constellation of physical findings that identify them as having a recognizable syndrome, such as craniofacial dysostosis (Crouzon's disease) or acrocephalosyndactyly (Apert's syndrome).

Although most clefts are thought to have a multifactorial derivation, the exact influence of a single gene abnormality, mendelian character, or teratogenic influences during pregnancy still warrant investigation. For this reason, a concerted effort must always be made to find any other associated congenital abnormalities and determine whether the cleft is part of a known syndrome. Deformities of the upper extremities are especially common in children with clefts. Families must be counseled regarding the cause and genetics of facial clefting and possible risks of recurrence.

Cleft lip alone or combined with a cleft of the palate has been reported to have a frequency of occurrence of about 1 per 1,000 live births. Men are affected more often than women, with the left side more commonly affected. Women have a higher incidence of isolated cleft palate. Feeding is sometimes difficult, and physicians, nurses, and parents need to develop innovative techniques.

Although several successful techniques have gained widespread acceptance, there is still controversy regarding the optimal timing for repair. In general, lip repair is

carried out when the patient is 10 weeks of age, weighs 4.5 kg (10 lb), and has a hemoglobin level of 100 grams per liter (10 grams per dl). The palate may be closed as early as 6 months to encourage the development of speech and preserve hearing. These children require serial examinations by an interdisciplinary team to detect associated problems and to develop a coordinated treatment plan. In the future we may see even earlier intervention for the correction of these problems using in utero techniques.

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Basal Cell Carcinoma

BASAL CELL CARCINOMAS, like the other radiation-induced skin cancers, are increasing in incidence, with an estimated 400,000 new cases diagnosed each year. The typical basal cell carcinoma appears as a shiny, pearl-white lesion that frequently has a central ulceration and surrounding telangiectasia. The borders are usually distinct, except for those of the morpheaform type, which spread diffusely with tentacle-like projections. Basal cell carcinomas virtually never metastasize and are most commonly superficial; however, they can be deeply invasive. These cancers invade local tissues by direct extension and cause both functional and aesthetic deformities. They may involve vital structures, such as the eye, or grow along embryonic fusion planes and invade the sinuses and brain.

Recent retrospective studies have shown that there are many effective methods for the treatment of basal cell carcinoma, with cure rates of greater than 94%. With the goal of obtaining adequate tissue margins with the best functional and aesthetic result, therefore, the current treatment of these skin cancers should be based on their size, depth, and histopathologic characteristics. Small (less than 2 cm) superficial basal cell lesions can be effectively treated with either electrodesiccation and curettage or cryosurgery, with cure rates of 95% and 97%, respectively. These are inexpensive and simple techniques that give good cosmetic results on the extremities and torso. Surgical excision in the relaxed skin tension lines with 0.5-mm margins is similarly effective, with cure rates of 94%, and frequently gives the best cosmetic result, particularly on the face. Mohs' micrographic surgery is recommended for basal cell carcinomas larger than 2 cm or those at higher risk for local recurrence or deep invasion, such as morpheaform tumors or lesions on the nose, ears, canthus, or eyelids. This technique of excision and microscopic examination of all margins has cure rates of 96% to 99% for primary tumors. In addition, Mohs' microsurgery has a similar cure rate for recurrent tumors, which is significantly better than the 60% to 70% cure rates with conventional therapy. Because the Mohs' procedure is time-consuming, more costly, and requires special training and a laboratory, it should be reserved for those difficult or recurrent tumors described earlier. After Mohs' microsurgery or surgical excision, the wound may be closed primarily with skin grafts or with local flaps for the best cosmetic result. If the lesion is extensive and at higher risk for local recurrence, the wound may be skin grafted or allowed to heal by contracture so that recurrences can be easily detected.

Radiation therapy, though not used routinely, is effective in treating basal cell carcinomas (90% to 94% cures) and can be used in old or debilitated patients. Topical 5-fluorouracil application is effective with multicentric superficial lesions. The retinoids and β-carotene have not shown efficacy in treatment or prevention.

Because ultraviolet radiation has a cumulative effect on the skin, the prevention of exposure cannot be overemphasized. It is estimated that the regular use of sunscreens could reduce the incidence of nonmelanoma skin cancers, most of which are basal cell, by 78%.

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Pressure Sores

PRESSURE SORES continue to be a common, expensive, and preventable complication of long-term immobility or paralysis. They develop in about 3% to 5% of all people admitted to a hospital and 45% of those in long-term-care facilities. More than 70% occur in patients who are 70 years and older. Factors placing patients at risk for ulceration are decreased mobility, activity, and sensory perception and an increase in friction, shear forces, and moisture. Because of the difficulty and expense of treatment, resources should be directed toward prevention. Foremost is the necessity to provide pressure relief in areas supporting body weight, particularly over regions of bony prominence. Limiting the duration of pressure and reducing peak pressures over particularly vulnerable sites can now be accomplished. Dynamic pressure devices can measure individual patterns of pressure variation, allowing customized mattress and cushion therapy. Friction can also be controlled by reducing or relieving pressure.

Ulcers are classified as grade I through IV. Grade I lesions are limited to the epidermis and superficial dermis. Damage from grade II lesions involves the full thickness of skin into adipose tissue. Grade III lesions extend through the skin, subcutaneous tissue, and into underly-

ing muscle. In grade IV lesions, all soft tissues are destroyed, with involvement of bone and vital structures. Wound infection is the most common complication, and osteomyelitis is frequently associated with full-thickness sores. In general, grade I and II ulcers are treated by local wound therapy and freedom from pressure. Grades III and IV often require surgical intervention. Repositioning and specialized air or foam mattresses as well as improving overall physical condition are important to patients with all grades.

The mainstay of established ulcer therapy is the provision of a pressure-free environment in concert with local wound care and serial surgical debridement to eliminate necrotic tissue and decrease the bacterial load. This may often be done at the bedside with simple instruments. Local anesthesia is seldom required. Ancillary factors requiring attention include adequate nutrition, the relief of continued spasticity, and the control of urinary and fecal incontinence. Psychosocial concerns, such as noncompliance, lack of self-care, and an inability to direct one's own care, must be addressed with both the family and the patient through intensive counseling and education. Antibiotic therapy is indicated only on evidence of infection—cellulitis, osteomyelitis, leukocytosis, fever, or bacteremia. Topical pharmacologic agents, such as hydrogen peroxide, povidone-iodine, and mafenide acetate, are adjuncts to be used with caution to avoid inhibiting healing by local toxicity.

Surgical closure for reasons of patient comfort, practicality, and long-term prevention are effective in more severe conditions. In some patients, such as those who are chronically ill or bedridden with multisystem disease or limited life expectancy, treatment goals may be to provide comfort rather than cure.

Numerous new wound care dressings have appeared to enhance the wound repair process in acute and chronic wounds. Well-designed controlled clinical trials are needed to differentiate between the beneficial effects of increased attention to the overall care of patients, including wound management, and the alleged salutary effects of the various dressing materials. The proper use of occlusive dressing in grade I and II ulcers can increase patient comfort and enhance healing.

There has been a shift in the past ten years toward an increasing use of muscle flap coverage for grade III and IV ulcers, which has decreased the number of operations and reduced the time to complete healing. Wound healing can now be enhanced by applying topical growth factors such as fibroblast growth factor B. The results of early clinical trials are encouraging in patients with large ulcers after surgical options have been exhausted. Electrical stimulation and biologic implants are other advanced experimental forms of therapy that may become more accessible and efficacious. Electrical stimulation has also been applied to treat secondary complications, including contracture, spasticity, deconditioning due to lack of exercise, and muscle atrophy.

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Laser Treatment of Skin Lesions

LASERS ARE USEFUL in the management of numerous disease processes including hemangiomas, nevi, benign and malignant skin neoplasms, and tattoos. When laser light is shown on living tissue, one or more of the following tissue reactions occur: reflection, scattering, transmission, or absorption. Tissue vaporization results from the absorption of light delivered with sufficient energy. The laser can produce a hemostatic incision, vaporize undesirable substances and tissue at the operative site, and coagulate blood vessels.

Capillary hemangiomas of infancy have been successfully treated using either the argon or the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser. It appears that the laser treatment of capillary hemangiomas of infancy produces a loss of surface vascularity, arrested growth, and early regression when compared with no therapy. Although treatment results from the Nd:YAG laser are superior to those of the argon laser, the incidence of complications is higher.

Patients with port-wine stains also respond well to laser treatment. In these cases, the argon laser seems to yield the best results. Young children have been thought not to be good candidates for laser treatment due to scarring created by the therapy. Recent evidence suggests, however, that 60% of children younger than 13 years have good to excellent results.

Many other lesions respond favorably to laser treatment. The argon laser successfully treats telangiectasias and venous lakes. Deep capillary or cavernous hemangiomas and those of the oral cavity may be best managed using the Nd:YAG laser. Tattoos can be removed by the carbon-dioxide laser, although some scarring of the overlying skin usually occurs.

Benign cutaneous pigmented lesions (actinic lentigines, senile lentigo, and café au lait spots) may be removed using the pulsed dye laser with the restoration of a nearly normal skin tone. A biopsy of a pigmented skin lesion to establish the diagnosis is necessary before initiating therapy.

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Alerts, Notices, and Case Reports

Peritoneal Coccidioidomycosis Diagnosed Incidentally at Herniorrhaphy

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INFECTION WITH THE pathogenic fungus, *Coccidioides immitis*, is a frequent event in areas endemic to this organism. Most infections are asymptomatic or remain localized to the lungs, and in only about 0.5% of host encounters with *C immitis* does the organism produce extrapulmonary symptoms.[1] In the Central Valley of California in the most recent 12-month period, there has been an outbreak of *C immitis* infections without historical parallel.[2] One uncommon presentation of *C immitis* infection is coccidioidal peritonitis. This disorder can present with diffuse abdominal pain or as an abdominal wall hernia.[3,4]

Report of a Case

The patient, a 30-year-old man, noticed periumbilical swelling three months before admission. Two months before admission, he detected a right inguinal swelling. He otherwise felt well without fever or constitutional symptoms. A chest x-ray film showed no abnormalities.

During an operation, an umbilical hernia was repaired without incident. During right inguinal herniorrhaphy, however, the hernia sac was found to be thickened and edematous. Straw-colored fluid was noted in the hernia sac, and this revealed a leukocyte count of 4.2×10^9 per liter (4,200 per μl), with 0.80 (80%) lymphocytes, 0.07 (7%) neutrophils, 0.01 (1%) basophils, 0.07 (7%) monocytes, and 0.01 (1%) mesothelial cells. Examination of the inguinal hernia sac revealed granulomata with *C immitis* spherules visible on Gomori-methenamine silver stain. Serologic studies for *Coccidioides immitis* revealed a complement-fixing antibody titer of 1:256. The patient did well with a course of intravenous amphotericin B colloidal dispersion.

Discussion

Coccidioidal peritonitis was first described in 1896 by Roxford and Gilchrist in an autopsy report,[5] and since that time, 13 cases of coccidioidal peritonitis have been reported. Curiously, as in our patient, 3 of 7 patients in the series of Saw and co-workers had no evidence of pulmonary disease, and 2 of these presented with right inguinal hernia.[3] In a review by Chen, 4 of 13 patients presented with uncomplicated inguinal hernia.[5]

Consideration to increasingly unusual presentations of coccidioidal infection should be given as the number of cases reaches epidemic proportions.

(Perez JA Jr, Arsura EL: Peritoneal coccidioidomycosis diagnosed incidentally at herniorrhaphy. West J Med 1993 Apr; 158:406)

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Acute Renal Failure Following Intravenous Streptokinase Infusion for Acute Myocardial Infarction

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STREPTOKINASE, ADMINISTERED EITHER intravenously or by the intracoronary route, is one of the drugs most frequently used for thrombolysis in acute myocardial infarction. Acute renal failure is a relatively rare complication following thrombolytic therapy with streptokinase.[1] We describe the case of a patient in whom acute renal failure developed nine days after thrombolytic therapy with streptokinase for acute inferior wall myocardial infarction.

Report of a Case

The patient, a 62-year-old man, was admitted to hospital because of acute inferior wall myocardial infarction. In the past he had had hypercholesterolemia and a diaphragmatic hernia. On physical examination he was in good general condition, his blood pressure was 130/80 mm of mercury, and his heart rate was 82 beats per minute. The lungs were clear, and there were no signs of

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heart failure. Laboratory test results on admission included a hemoglobin level of 141 grams per liter (14.1 grams per dl), a leukocyte count of 8.3×10^9 per liter (8,300 per μl), urea nitrogen 6.1 mmol per liter (17 mg per dl), and creatinine 114 μmol per liter (1.3 mg per dl). Two hours after the onset of chest pain, 1.5 million units of streptokinase was given intravenously with relief of the chest pain and resolution of the ST elevation within an hour. Oral aspirin, 250 mg per day, and a continuous intravenous infusion of heparin and isosorbide dinitrate

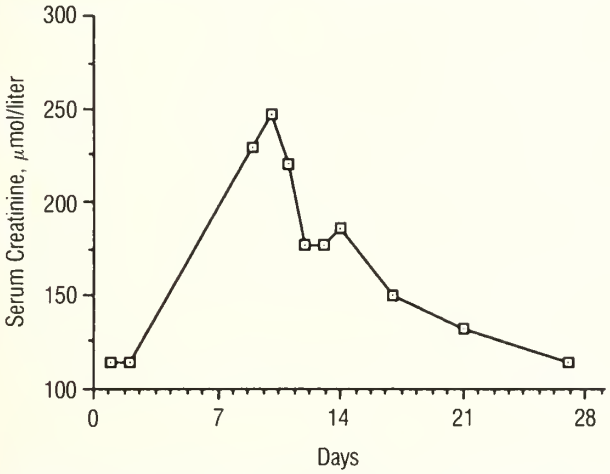

Figure 1.—The graph shows the relation between the serum creatinine concentration and time after streptokinase was administered.

were administered for two days. During his hospital stay he was hemodynamically stable, without hypotension, arrhythmia, renewed ischemia, or evidence of blood loss. He did not receive any other medication during his hospital admission.

On the ninth day he complained of nausea and fatigue. An electrocardiogram did not reveal signs of recurrent ischemia. A laboratory investigation showed an erythrocyte sedimentation rate of 110 in the first hour and an elevation of the serum creatinine level to 230 μmol per liter (2.6 mg per dl) and of urea to 8.9 mmol per liter (25 mg per dl) (Figure 1). Examination of the urine revealed proteinuria (2+), 10 to 15 erythrocytes, and 2 to 5 leukocytes per high-power field. A few waxy and granular casts were seen. During the following day a diffuse purpuric rash and arthralgia developed. The serum creatinine level rose to 247 μmol per liter (2.8 mg per dl). The results of serum protein immunoelectrophoresis were normal, and tests for rheumatoid and antinuclear factors were negative. Tests for antibasement membrane, antismooth muscle and antimitochondrial antibodies were negative. A serum C3 level was 1.01 grams per liter (normal value for our laboratory, 1.00 to 1.50) and serum C4 level 0.18 grams per liter (normal, 0.15 to 0.25). A test for hepatitis B surface antigen was negative. Echocardiography did not demonstrate a mural thrombus or vegetations. An ultrasound examination showed normal-sized kidneys without hydronephrosis, and a radionuclide renal scan did not show a perfusion defect or evidence of obstruction. A skin biopsy revealed vasculitis, and immunofluorescent staining disclosed immunoglobulin (Ig) A, IgM, C3, and fibrinogen.

A regimen of hydration with an intravenous infusion of saline solution was initiated. On the following days, his serum creatinine level gradually fell to 133 μmol per liter (1.5 mg per dl) and the urea concentration to 7.1 mmol per liter (see Figure 1), the nausea and fatigue disappeared, and the arthralgia and rash resolved. During the episode he remained afebrile; his blood pressure was between 110/70 and 120/80 mm of mercury, and he passed from 4.75 to 5.0 liters of urine per day. The patient said he had not had tonsillitis or a skin infection during the six months before his admission, and he had never received streptokinase before this admission. During a follow-up of six months he remained asymptomatic, without deterioration of renal functions.

Discussion

This patient had a systemic complication nine days after a single dose of streptokinase infusion given for acute myocardial infarction. The clinical manifestation included purpuric rash, arthralgia, and transient acute renal failure, all of which resolved spontaneously within three weeks. These symptoms are compatible with a serum sickness-like disease.

The differential diagnosis of acute renal failure following thrombolytic therapy with streptokinase is presented in Table 1.

Conditions causing hypotension or low cardiac output may induce prerenal azotemia and acute tubular necrosis. Myocardial infarction alone may cause hypotension and a low-output state by several mechanisms: left ventricular failure, right ventricular infarction, acute mitral regurgitation, ventricular septal defect, tamponade, and arrhythmia. Transient hypotension at the time of streptokinase infusion is observed in about 10% of patients with acute myocardial infarction,[1,2] although the effect is usually short-lived (< 10 minutes).[3] The hypotensive effect can

TABLE 1.—*The Differential Diagnosis of Acute Renal Failure Following Streptokinase Therapy for Acute Myocardial Infarction*

Ischemic injury
Low cardiac output or hypotension
Related to the myocardial infarction itself
Direct effect of streptokinase
Reperfusion-induced hypotension
Hemorrhagic shock
Emboli from mural thrombus
Cholesterol emboli syndrome
Myoglobinuria
Immunologic injury
Serum sickness
Schönlein-Henoch purpura
Immune complex nephritis (crescentic?)
Postrenal obstruction
Retroperitoneal hemorrhage
Clots in ureters

lead to ischemic damage to the kidneys, especially in patients with preexisting renal disease, renovascular narrowing, and in patients aged 65 and older. Kalra and coworkers described the case of a patient with acute inferior wall myocardial infarction in whom acute tubular necrosis developed that was attributed to the hypotensive effect of streptokinase.[4] Transient hypotension and bradycardia may be caused by reperfusion with successful thrombolysis.[5] Major bleeding is a common complication of thrombolytic therapy[1] and may lead to hypovolemic shock and acute tubular necrosis.

A possible mechanism of acute renal failure is the dislodgment of renal artery emboli from a myocardial mural thrombus by the thrombolysis.[6,7] Even in patients with two functioning kidneys, unilateral embolism occasionally causes acute renal failure and oliguria.[8] Cholesterol emboli after streptokinase infusion were described in two patients treated for venous thrombosis[9,10] and in three patients with acute myocardial infarction.[11,12] In those patients the syndrome developed within two days after streptokinase infusion. Physical examination revealed livedo reticularis[9] and extensive ulcerating ecchymosis.[12] An additional cause of renal complication was described in two patients treated for thrombotic or thromboembolic occlusion of the leg: massive myoglobinuria following reperfusion induced acute tubular necrosis.[13]

Acute renal failure caused by immunologic mechanisms after streptokinase therapy may be divided into three forms:

• A serum sickness-like syndrome complicating streptokinase use was described.[14] There are few reports of acute renal failure complicating a serum sickness-like disease following prolonged streptokinase infusion for venous thromboembolism[15,16] or peripheral artery thrombosis,[17] although direct evidence of the deposition of immune complexes in renal biopsy specimens was not described. The continuous infusion may result in a more prolonged availability of circulating streptokinase, allowing time for the formation of antigen-antibody complexes in antigen excess and, thus, the development of immune complex disease.[18] Despite vast experience with streptokinase therapy for acute myocardial infarction, only five cases of serum sickness and renal impairment following a short course of streptokinase infusion for acute myocardial infarction have been described.[19-23] One patient had a history of severe cellulitis of the leg 13 years before the myocardial infarction,[23] and another had had rheumatic fever 47 years before the myocardial infarction.[19] Two other patients received a second dose of streptokinase 2.5 and 4 days after the first dose.[20,21] In only one other patient with no history of streptococcal infection, the serum sickness phenomenon was noted after a single dose of streptokinase, as was the case in our patient.[22] The clinical and laboratory findings of the patients are presented in Table 2.

The renal impairment appeared shortly after the second dose in the two patients with rechallenge and six to nine days after streptokinase therapy in the patients without previous sensitization. Fever was reported in four patients, rash in five patients, and arthralgia or arthritis in four patients. The findings on urinalysis were variable and included proteinuria, erythrocytes and leukocytes, and waxy and granular casts. Levels of C3 and C4 were measured in five patients, and all were within the normal range. An assay of CH_{50} was done in two patients: in one the level was low,[23] and in the other it was normal.[20] Hypocomplementemia is a common but not invariable finding in serum sickness.[24] Transient elevations of complement levels may accompany myocardial infarction, however, so the absence of hypocomplementemia does not exclude the diagnosis of serum sickness.[25] Serum immune complexes were measured in two patients: in one the test result was negative,[20] and in the other it was positive.[23] A renal biopsy in one patient revealed acute tubular necrosis with structurally normal glomeruli and weak, granular, mesangial deposition of IgA, IgM, and C3.[23] In all the patients, symptoms resolved and serum creatinine levels returned to baseline within 12 days.

• Vasculitis, resembling Schönlein-Henoch purpura, associated with streptokinase therapy for acute myocardial infarction was described in three patients.[26-28] In one of them, acute renal failure developed ten days after a single dose of streptokinase.[28] A renal biopsy showed modest segmental mesangial hypercellularity and mesan-

TABLE 2.—*Clinical and Laboratory Data of Patients With Renal Impairment, Caused by Serum Sickness, After Streptokinase Therapy for Acute Myocardial Infarction*

Source	*Age, yr*	*Sex*	*Previous Streptococcal Infection*	*Readministration*	*Day to ARF**	*Fever*	*Rash*	*Arthralgia*	*Urinalysis Results*
Alexopoulos et al, 1984[19]	58	♂	RF	No	6	Yes	Yes	Yes	RBCs, WBCs
McGrath et al, 1985[20]	62	♂	No	Yes	5.5†	Yes	Yes	Yes	RBCs, proteinuria
Chan et al, 1988[21]	65	♂	No	Yes	4†	No	No	No	WBCs, proteinuria, and granular casts
Payne et al, 1989[22]	70	♂	No	No	8	Yes	Yes	Yes	Proteinuria
Davies et al, 1990[23]	52	♂	Yes	No	3	Yes	Yes	Yes	RBCs, granular casts, and proteinuria
This report	62	♂	No	No	9	No	Yes	Yes	Proteinuria, RBCs, granular casts

RBCs = erythrocytes, RF = rheumatic fever, WBCs = leukocytes

*Days from the first dose of streptokinase to beginning of acute renal failure (ARF).
†Acute renal failure developed 3 and 1 days, respectively, after the second dose of streptokinase.

gial expansion. Glomeruli demonstrated pronounced granular staining with prominent IgA deposition.

• Murray and colleagues described the case of a patient with crescentic glomerulonephritis that developed 2 weeks after a β-hemolytic streptococcal throat infection and 33 days after streptokinase therapy for myocardial infarction.[29] They postulated that the previous sensitization by the streptokinase facilitated the hypersensitivity reaction to the streptococcal infection.

Retroperitoneal hematoma induced by streptokinase may press and obstruct the ureters, as may massive hematuria and blood clots.[30]

Conclusion

Acute renal failure following streptokinase therapy for acute myocardial infarction is a relatively rare complication of thrombolytic therapy. The cause may be related to the infarction itself or to special effects of the streptokinase. When the disease is progressive, a renal biopsy may occasionally be indicated for diagnosing potentially treatable glomerular disease such as rapidly progressive glomerulonephritis.

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Acute Leukemia Associated With Mediastinal Germ Cell Tumor

De Novo Versus Therapy-Related Leukemia

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AGGRESSIVE MULTIMODALITY treatment of malignant diseases has resulted in a pronounced improvement in survival and even cure in patients with different types of cancer, such as Hodgkin's disease, non-Hodgkin's lymphoma, and germ cell tumor. The problem of secondary malignancy is of concern, however. An increase in the incidence of acute leukemia, predominantly myeloid type, is noted in patients who are cured of a primary malignant lymphoma, ovarian carcinoma, or germ cell tumor. The association of germ cell tumor with acute leukemia has been described.[1-4] We report a case of trisomy 8 acute monocytic leukemia occurring 20 months after the diagnosis and treatment of mediastinal germ cell tumor. We discuss the possible causes of the association between germ cell tumor and acute leukemia and the use

(Keung YK, Liang R, Chiu EKW: Acute leukemia associated with mediastinal germ cell tumor—De novo versus therapy-related leukemia. West J Med 1993 Apr; 158:409-412)

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of cytogenetic studies in the diagnosis of therapy-related leukemia.

Report of a Case

The patient, a 23-year-old man, presented initially in September 1986 with general malaise, fever, and dry cough for three weeks. A chest x-ray film showed an anterior mediastinal mass with a secondary deposit in the lingular lobe of the left lung. A thoracotomy was done with excision of the mediastinal mass and wedge resection of the lingular lobe. The histologic diagnosis was nonseminomatous mixed germ cell tumor with elements of endodermal sinus tumor and embryonal carcinoma. A preoperative α-fetoprotein level was not available, but a postoperative level was more than 800 μg per liter (800 ng per ml), and an assay for the β-human chorionic gonadotropin was negative. He was subsequently referred to our unit for further management.

On physical examination on referral, both testicles appeared normal. A computed tomographic (CT) scan of the abdomen showed normal-sized liver, spleen, and retroperitoneal lymph nodes. There was no intra-abdominal mass. The α-fetoprotein level rose to 38,090 μg per liter. A regimen of cisplatin, 120 mg per m^2 of body surface, and etoposide (VP-16-123), 100 mg per m^2 for five days every two to three weeks, was started. The α-fetoprotein level dropped to normal after three courses of chemotherapy. After the fifth course of chemotherapy, however, a solitary nodule appeared in the right upper lung field, and the patient had repeated episodes of septicemia. A right upper and middle lobectomy was done in March 1987. On histologic examination, the mass showed empyema with a thickened fibrous wall. There was no evidence of residual disease. Two more courses of cisplatin and etoposide were given after the operation, with a total cisplatin dose of 840 mg per m^2 and the total etoposide dose of 3,500 mg per m^2.

The patient attended for regular follow-up visits and had follow-up CT scans performed every three to four months with no evidence of recurrence. He was asymptomatic until April 1988, when a small suprapubic skin abscess developed. The leukocyte count was found increased to 102×10^9 per liter with 0.85 immature monocytes and 0.03 blasts, a hemoglobin level of 107 grams per liter (10.7 grams per dl), and a platelet count of 21×10^9 per liter. On physical examination, he had low-grade fever, hypertrophy of the gums, and shotty cervical lymph nodes. The liver and spleen were not enlarged. A bone marrow examination confirmed the diagnosis of acute monocytic leukemia, French-American-British classification M5b, with immature monocytes and blasts constituting about 45% of the nucleated cells in the marrow. Both erythropoietic and megakaryocytic series were markedly depressed. Cytogenetic study of the bone marrow aspirate showed trisomy 8 as the sole abnormality. The serum lysozyme level was elevated to 9,000 units per ml. The α-fetoprotein level remained normal. Induction chemotherapy was given in May 1988 consisting of an infusion of cytarabine, 100 mg per m^2 per day for seven days, daunorubicin hydrochloride, 50 mg per m^2 per day for three days, and etoposide, 75 mg per m^2 per day for seven days. The disease, however, was refractory to the treatment, and the patient died of uncontrolled leukemia in June 1988.

Discussion

Both leukemia and germ cell tumor are rare diseases, and the development of leukemia following germ cell tumor is unlikely to be coincidental. The leukemia more likely developed as part of the natural history of germ cell tumor or was therapy related.

There is evidence suggesting that malignant tumors may arise from different components of germ cell tumor.[5] The most frequent histologic type of such tumor is embryonal rhabdomyosarcoma, followed by nephroblastoma, chondrosarcoma, and adenocarcinoma. Similar events may have occurred for leukemia. Larsen and co-workers have reported the case of a patient with mediastinal germ cell tumor who was treated with chemotherapy followed by the resection of residual mediastinal tumor.[6] The resected tumor contained a population of mononuclear cells with the histologic features of lymphoblasts. Three months later, acute lymphoblastic leukemia developed. It was suggested that the lymphoblastic leukemia originated from the mediastinal germ cell tumor. Chaganti and Ladanyi and associates also reported the cases of three patients with mediastinal germ cell tumor in whom acute nonlymphocytic leukemia subsequently developed.[7,8] The authors were able to demonstrate the presence of isochromosome i(12p) in all the primary tumor and leukemic clones, suggesting the leukemia was derived from primary germ cell tumor. Oosterhuis and colleagues, however, could not confirm this finding in their patient.[9]

In a review of the literature, 30 patients had the development of leukemia simultaneously with or subsequent to a diagnosis of germ cell tumor, of whom 13 had mediastinal germ cell tumor.[1] When these data are compared with the fact that mediastinal germ cell constitutes only 1% to 5% of all germ cell tumors in humans, it is not difficult to appreciate the particular tendency of patients with mediastinal germ cell tumor to have acute leukemia develop after treatment. Recent follow-up studies further confirm the association of malignant hematologic disorders, especially acute megakaryocytic leukemia and malignant histiocytosis, with mediastinal germ cell tumor.[10] Nichols and co-workers postulated that the anatomic location within mediastinum might confer a particularly favorable microenvironment or growth factors may be elaborated, causing the malignant transformation of the multipotential germ cell within the tumor.

An adverse effect of chemotherapy is the other possible mechanism for the association of acute leukemia and germ cell tumor. It is known from studies of animals that cisplatin is both mutagenic and carcinogenic.[11] There have been several reports of cisplatin therapy-related leukemia occurring.[12-15] One of the authors also had a patient with small-cell carcinoma of the lung who was

treated primarily with cisplatin and etoposide. The patient died four years later of therapy-related myelodysplasia transforming to acute myeloid leukemia with multiple karyotypic abnormalities and without any clinical evidence of primary small-cell lung carcinoma.

Etoposide therapy has also recently been implicated in therapy-related leukemia.[16-20] Recent data by Pedersen-Bjergaard and co-workers suggested an increased risk of myelodysplasia and leukemia after receiving etoposide, cisplatin, and bleomycin for germ cell tumor.[17] In their report, four cases of acute myeloid leukemia and one case of myelodysplasia occurred in a cohort of 212 patients with germ cell tumors treated with etoposide, cisplatin, and bleomycin. No leukemia was detected in a cohort of 127 patients previously treated with cisplatin, bleomycin, and vinblastine. The leukemia risk was also dose-related with no leukemia observed in those receiving a cumulative etoposide dose of less than 2,000 mg per m^2. Three leukemic patients had balanced chromosome translocation involving bands 11q23 or 21q22, which are characteristic for leukemia and myelodysplasia following treatment with etoposide. Pui and associates recently also showed that children with acute lymphoblastic leukemia who were treated with etoposide were at a higher risk of secondary acute myeloid leukemia developing.[19] They further showed that this risk is strongly associated with a weekly or twice-a-week dosing schedule.[20] Hence, there is no doubt that the chemotherapy commonly used for germ cell tumor can induce leukemia.

Therapy-induced leukemia, especially after the use of alkylating agents, is usually characterized by the presence of an antecedent hematologic disorder or a preleukemic phase, a trilineage dysplasia, frequent cytogenetic abnormalities, an ominous prognosis, and a poor response to antileukemic therapy.[21-24] The time interval from the initial treatment to the development of secondary leukemia or myelodysplasia is highly variable, ranging from several months to more than 20 years, with a median interval of five to six years. Those cases associated with etoposide therapy are typically without preceding myelodysplasia and with a short latency period.[16] The time interval from the initial treatment to the development of leukemia is not a useful index to distinguish de novo leukemia from therapy-related leukemia. A more reliable diagnostic tool is a cytogenetic study. Chromosome numbers 5 and 7 abnormalities are often seen in patients with therapy-related leukemia after receiving alkylating agents and chromosome 11q23 or 21q22 rearrangement in leukemia after the use of epipodophyllotoxins such as etoposide. Trisomy 8 is found in 36% of patients with acute nonlymphocytic leukemia. It also was seen more frequently in patients with leukemia associated with a previous malignant neoplasm or cytotoxic therapy.[22,25-27] In the 1990 article from Nichols and associates, trisomy 8, −5, and −7 were present in four of ten patients with hematologic malignant disorders and mediastinal germ cell tumors and in whom cytogenetic studies were done.[10]

Whether our patient's leukemia was therapy-related or de novo is difficult to establish. The relatively short interval between the treatment of germ cell tumor and the occurrence of leukemia did not exclude the possibility that it was related to the chemotherapy. On the contrary, it could be consistent with epipodophyllotoxin-induced leukemia.

With the evidence presented so far, the association of mediastinal germ cell tumor and hematologic cancer is well established. The mechanism of this association is far from clear, however. Our speculation is that a certain portion of the germ cell tumor contains a possible leukemogenic clone that manifests itself only when the patient survives long enough or that this leukemogenic clone is particularly susceptible to a leukemia-inducing effect of chemotherapy. The particular tendency for leukemia to develop in patients with primary mediastinal germ cell tumors may indicate a certain permissive role played by the mediastinum probably by the elaboration of appropriate growth factors. The association with the extremely rare acute megakaryocytic leukemia is interesting and unexplained. Detailed cytogenetic studies should be done on all patients with germ cell tumors, especially mediastinal. These patients should be observed closely for any occurrence of hematologic cancer so that appropriate cytogenetic and cell culture studies can be done promptly.

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Severe Angioedema and Respiratory Distress Associated With Lisinopril Use

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ANGIOTENSIN-CONVERTING ENZYME (ACE) inhibitors are frequently used as first-line agents for the treatment of hypertension. Angioedema is a recognized but infrequent adverse effect of therapy, with a reported frequency between 0.1% and 0.2%.[1] Slater and co-workers analyzed 177 cases of angioedema associated with the use of enalapril maleate.[2] These cases were identified during clinical trials and postmarketing surveillance studies and from spontaneous reports of adverse reactions during postmarketing use. Of these 177 cases, 38 (22%) were classified as life-threatening, with patients having respiratory symptoms that included dyspnea, laryngeal swelling, laryngospasm, or stridor. Only 4 of the 177 patients (2.3%) required intubation, and all survived their episode of angioedema. Thus, severe angioedema producing respiratory compromise is rare (0.2% × .22) with an incidence of 0.044%, or 44 cases per 100,000 patients. Severe angioedema requiring intubation is extremely rare (0.2% × .023) with an incidence of 0.0023% to 0.0046%, or 2.3 to 4.6 cases per 100,000 patients. Most episodes occur within the first week after starting therapy but have been reported to occur as long as two years after the initiation of therapy.[3-9]

Although experience with lisinopril, one of the newer nonsulfhydryl-containing ACE inhibitors, is limited, the incidence of angioedema associated with its use should parallel that of other long-acting agents such as enalapril and should also be about 0.2%. Over the past 21 months, we have been involved with the management of four patients in whom severe upper airway angioedema with or without respiratory distress developed associated with lisinopril therapy. Three of these patients required intubation for airway management. This represents a notably higher incidence of severe angioedema than expected from experience with other ACE inhibitors. The following report summarizes our experience with these cases.

Report of Cases

Case 1

The patient, a 50-year-old man with a history of asthma, long-standing hypertension complicated by end-stage renal disease requiring hemodialysis three times a week (baseline serum creatinine level, 486 μmol per liter [5.5 mg per dl]), and β-lactam antibiotic hypersensitivity, presented with massive tongue angioedema. He has had oropharyngeal edema associated with cephradine therapy that did not require intubation and that resolved with the administration of steroids and drug cessation. Over the past year and a half, his blood pressure control regimen included captopril and then enalapril. Two months before admission, lisinopril, 10 mg daily, was substituted for enalapril.

On the morning of admission, the patient took his usual medications: lisinopril, 10 mg; theophylline, 300 mg; and calcium carbonate, 4,800 mg. About two hours later, he noted swelling of his tongue. There was no pruritus, dyspnea, stridor, or associated symptoms. The similarity between this episode and the cephradine-associated angioedema prompted the patient to seek medical attention. In the emergency department, where he had progressive lingual edema and increasing difficulty with articulation, he was intubated. On physical examination after intubation, he had a blood pressure of 190/100 mm of mercury with a heart rate of 104 beats per minute and massive angioedema localized to the tongue, excluding the lips and the rest of the face (Figure 1); there were scattered urticarial lesions on the body, but the lungs were clear to auscultation. Before intubation and with the patient breathing 50% oxygen by face mask, arterial blood gas measurements showed a pH of 7.31, a Pa_{O_2} of 153 mm of mercury and a Pa_{CO_2} of 37 mm of mercury. A leukocyte count was 6.9×10^9 per liter (6,900 per μl) without eosinophilia. Complement C3, C4, and total complement levels determined three days after admission

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Figure 1.—Left, Patient 1 is shown shortly after intubation for massive angioedema of the tongue. **Right,** A close-up view shows the massive lingual edema; the patient was unable to retract his tongue into his mouth.

were normal. Treatment was started with two 0.3-ml doses of subcutaneous epinephrine (1:1,000); 5 ml of intravenous epinephrine (1:10,000); diphenhydramine hydrochloride, 50 mg given intravenously every 8 hours; hydrocortisone sodium succinate, 100 mg given intravenously every 6 hours; nebulized albuterol treatments every 4 hours; and ranitidine hydrochloride, 50 mg given intravenously every 24 hours. Lisinopril was discontinued, but the other medications were continued at their regular dosages. No other triggering factors could be identified except the lisinopril. The angioedema resolved over the next 48 hours, and the patient was extubated without any problems. He was discharged on a regimen of prednisone, with the dose tapered over two weeks.

Case 2

The patient, a 68-year-old man, has a history of hypertension, chronic renal insufficiency (baseline serum creatinine level, 248 μmol per liter [2.8 mg per dl]), and anemia of chronic disease. He has no known allergies, food hypersensitivity, or history of idiopathic anaphylaxis. Lisinopril, 10 mg daily, was added to his medication regimen about four weeks before admission. On the day of admission, the patient took his morning medications as usual: lisinopril, 10 mg; prazosin hydrochloride, 2 mg; indapamide, 2.5 mg; nifedipine, 20 mg; and 1 tablet of a multivitamin supplement. About two hours later, he noted oropharyngeal edema without pruritus, dyspnea, or stridor. He went to the emergency department where he had a blood pressure of 176/96 mm of mercury with a heart rate of 110 beats per minute. On physical examination he had pronounced oropharyngeal edema, including the tongue, and normal pulmonary findings. A leukocyte count was 8.7×10^9 per liter (8,700 per μl) without eosinophilia. The patient was admitted to the intensive care unit where he received diphenhydramine, 50 mg given intravenously every 6 hours; methylprednisolone sodium succinate, 60 mg given intravenously every 6 hours; and ranitidine, 50 mg intravenously every 12 hours. Complement C3 and C4 levels measured two days after admission were normal. He did not require intubation, and his angioedema and symptoms resolved within 24 hours. He has not had any recurrence of angioedema since lisinopril therapy was discontinued.

Case 3

The patient, a 68-year-old man with adult-onset diabetes mellitus and hypertension, was admitted to the medical intensive care unit because of a cerebrovascular accident and a subendocardial myocardial infarction. He has no known allergies, food hypersensitivity, or a history of idiopathic anaphylaxis. A regimen of lisinopril, 10 mg daily, was started for blood pressure control, and the dosage was subsequently increased to 20 mg daily. A week later, the patient had an episode of severe respiratory distress. His blood pressure was 160/110 mm of mercury, with a heart rate of 120 beats per minute and a respiratory rate of 36 breaths per minute and accessory muscle use; arterial blood gas determination with the patient receiving 100% oxygen by face mask showed a pH of 7.39, a Pa_{O_2} of 280 mm of mercury, and a Pa_{CO_2} of 39 mm of mercury. He was markedly dyspneic and had chest tightness but no wheezing. He was emergently intubated and treated with a course of methylprednisolone, 60 mg given intravenously every six hours. His dyspnea abated, and he was extubated a day later. Eight hours after extubation, however, increasing tachypnea and stridor developed, and he was reintubated. He was given methylprednisolone, 60 mg intravenously every six hours, which was changed to prednisone, 40 mg a day, over the next three days. He was able to be extubated four days later. Prompted by concern over the stridor and a possible upper airway lesion, he underwent airway inspection with a flexible fiber-optic bronchoscope at the time of extubation. Examination revealed only mild vocal cord edema and erythema attributed to his intubation but no site or other evidence of upper airway obstruction.

The prednisone dosage was rapidly tapered from 40 mg a day to 10 mg a day over five days. The lisinopril dosage was increased to 30 mg a day for blood pressure control. A urinary tract infection developed, and a regimen of ampicillin, 1 gram given intravenously every six hours, and gentamicin sulfate, 80 mg every eight hours,

was started. Five days later, the patient had another episode of respiratory distress, associated with stridor and a truncal rash. His blood pressure was 160/100 mm of mercury with a heart rate of 118 beats per minute and a respiratory rate of 40 breaths per minute. Arterial blood gas measurements with the patient breathing room air showed a pH of 7.41, a Pa_{O_2} of 97 mm of mercury, and a Pa_{CO_2} of 52 mm of mercury, with a leukocyte count of 5.9×10^9 per liter (5,900 per μl) and no eosinophilia. The serum creatinine level during both episodes of respiratory distress was 141 μmol per liter (1.6 mg per dl). He was emergently intubated, and the use of both lisinopril and ampicillin was discontinued. Treatment with methylprednisolone, 60 mg intravenously every six hours, and nebulized racemic epinephrine was started. He improved, was extubated two days later, and transferred to the medical ward on a short course of prednisone. His first episode of respiratory distress was probably related to lisinopril use, with symptoms attenuated by steroid therapy. This episode was also not recognized as an adverse reaction to medication, and he continued to receive lisinopril. As the steroid dosage was tapered and the lisinopril dosage increased, his respiratory symptoms recurred, although the relationship between lisinopril therapy and the second episode of respiratory distress is clouded by the concomitant use of ampicillin. No other agents were identified as possible triggers of his respiratory distress, and there has been no recurrence since lisinopril therapy was discontinued.

Case 4

The patient, a 63-year-old man with a long history of coronary artery disease and hypertension, was admitted for the management of poorly controlled hypertension. He had no known allergies, food hypersensitivity, or history of idiopathic anaphylaxis. He responded to therapy, and lisinopril, 10 mg per day, was added to his regimen of nifedipine and isosorbide dinitrate. Four days after beginning lisinopril use, he awoke at 2 AM with a sensation of increasing nasal and upper airway congestion. He used an over-the-counter nasal spray—oxymetazoline hydrochloride and benzalkonium chloride—without relief. Over the next half hour, he noted increasing right-sided jaw and facial swelling and neck fullness and felt increasing dyspnea. He came to the emergency department where he was noted to be in mild respiratory distress with a blood pressure of 160/100 mm of mercury, a heart rate of 84 beats per minute, and a respiratory rate of 20 breaths per minute. He described a sensation of suffocation and had moderate right-sided facial, jaw, and lip swelling, with clear lungs. He was thought to have had an anaphylactic reaction to the nasal spray and was given 0.5 ml of subcutaneous epinephrine (1:1,000), diphenhydramine, 25 mg intramuscularly, and methylprednisolone, 125 mg intravenously, and admitted to the intensive care unit for further therapy.

Therapy was instituted with diphenhydramine, 50 mg intravenously every six hours, and methylprednisolone, 60 mg intravenously every six hours. Laboratory studies included an arterial blood gas determination with the patient breathing 2 liters of oxygen per minute, showing a pH of 7.39, a Pa_{CO_2} of 34 mm of mercury, and a Pa_{O_2} of 85 mm of mercury. The leukocyte count was 12.5×10^9 per liter (12,500 per μl) without eosinophilia. The serum creatinine level was 168 μmol per liter (1.9 mg per dl; previously, 141 μmol per liter [1.6 mg per dl]). He also received a 10-mg dose of lisinopril on the morning of admission. He appeared to be stable and underwent videolaryngoscopy, which revealed swelling of the supralaryngeal structures and supraglottic edema (Figure 2).

Figure 2.—Videolaryngoscopy of patient 4 shows supraglottic tissue swelling and edema partially overlying the vocal cords (photograph provided by Bruce Gerratt, PhD, Audiology and Speech Pathology Service, Department of Veterans Affairs Medical Center, Los Angeles, California).

Over the next eight hours, the swelling progressed to involve both sides of his face and the right side of his tongue, and stridor was also noted. At that time he was endotracheally intubated. The leukocyte count was repeated and was 21.9×10^9 per liter (21,900 per μl) without eosinophilia. Cimetidine, 300 mg intravenously every six hours, was added to his regimen. Lisinopril use was discontinued. He had gradual resolution of his facial edema and was able to be extubated three days later. No other agents were identified as possible triggers of his angioedema.

In summary, four cases of severe angioedema with or without respiratory distress associated with lisinopril use were identified at our institution between December 1989 and August 1991. Pharmacy medication records, which are computerized and therefore complete, indicate that 9,790 prescriptions for lisinopril were written for 3,926 patients during this time period. This represents an incidence of 0.1% for severe angioedema, which is significantly ($P < .01$) higher than the expected incidence of 0.0046% extrapolated from existing data.

Discussion

Lisinopril is one of the newer angiotensin-converting enzyme inhibitors available in the United States. It is more potent with a longer duration of action than either captopril or enalapril. It is excreted unchanged in the urine and feces, in contrast to captopril or enalapril, both

of which are metabolized before elimination. Lisinopril reaches a peak serum concentration between six and eight hours after an oral dose and achieves steady-state levels in two to three days.[10]

Angioedema is a recognized but infrequent adverse effect of therapy with all ACE inhibitors. Most episodes of angioedema reported occurred within the first week of therapy, but there are reports of angioedema as long as two years after the initiation of therapy.[3-9] The frequency of angioedema associated with lisinopril is reported to be 0.1% (package insert, Zestril, ICI Pharmaceutical Group, Stuart Pharmaceuticals), but severe, life-threatening angioedema has an even lower frequency. The expected incidence of severe angioedema is probably less than 50 per 100,000 patients, and the expected number of patients requiring intubation for severe angioedema is probably less than 5 per 100,000. These calculations were based on data obtained during clinical trials and from adverse reaction reports. They represent the experience of a large number of physicians, and the definition of respiratory compromise is subject to some interpretation and therefore imprecision. Intubation, however, is a well-defined clinical outcome and allows a more precise estimate of severe respiratory compromise. The actual incidence is probably higher because of inherent underreporting in a passive surveillance system and because many drug reactions go unrecognized. This represents the reported experience with captopril and enalapril. The experience with severe angioedema associated with lisinopril use has not been well documented.

The largest clinical experience with lisinopril was reported by Rush and Merrill.[11] In their evaluation of a series of 1,476 patients—1,165 with hypertension, 311 with congestive heart failure, and 211 normal volunteers—angioedema was reported in 5 (0.4%) hypertensive patients, 2 (0.6%) patients with congestive heart failure, and in none of the normal volunteers. The angioedema was considered severe enough to necessitate discontinuing the lisinopril use in only one of the hypertensive patients and in one of the patients with congestive heart failure. No patient had life-threatening angioedema. The angioedema was felt to be mild in the rest of the patients, and lisinopril use was either continued or discontinued until swelling resolved and the drug was reinstituted.

Orfan and co-workers reported the cases of two patients in whom angioedema developed shortly after lisinopril therapy was started.[12] One patient had upper airway edema develop with partial airway compromise, but this responded to medical therapy. The other patient did not have respiratory symptoms. In this small series, a history of idiopathic angioedema was noted in both patients and may reflect an underlying predisposition for the development of angioedema.

We report four cases of severe life-threatening angioedema, with or without respiratory distress, associated with lisinopril therapy. The overwhelming majority of prescriptions are filled by our pharmacy. Because our center is a Department of Veterans Affairs Medical Center, our patient population is a fairly closed one, and relatively few veterans served by our system are admitted to hospitals elsewhere. This allows a reliable determination of the numerator and denominator when assessing adverse drug effects. Therefore, our experience probably accurately reflects the incidence of severe angioedema associated with lisinopril use. Altered drug elimination in patients with renal impairment and continued drug administration because of an unrecognized drug reaction are two possible explanations for these cases.

Pharmacokinetics studies have demonstrated the accumulation of lisinopril in patients with renal insufficiency.[13,14] In patients with severe renal impairment (creatinine clearance < 0.5 ml per second [30 ml per minute]), a 12-fold increase in the serum concentration of lisinopril was noted compared with patients with normal renal function, and a 6-fold increase was noted compared with patients with mild renal impairment (creatinine clearance of 0.5 to 1.3 ml per second [30 to 80 ml per minute]) after a single 5-mg dose.[14] In patients with severe renal impairment, the time to peak concentration was longer, the peak concentration was higher, and the decline in serum concentration slower than in patients with normal renal function. These investigators noted no increase in adverse effects or problems with hypotension in their patients, but the sample size was small (n = 6). A higher incidence of first-dose hypotension has occurred in hypertensive patients with mild renal impairment (serum creatinine level > 141 μmol per liter [1.6 mg per dl]) compared with patients with normal renal function.[11]

Others have noted angioedema associated with the use of other ACE inhibitors in patients with renal impairment. Suarez and associates reported two cases of captopril-associated angioedema in patients with severe renal impairment.[15] The first patient was receiving dialysis, and facial and periorbital edema developed after eight weeks of captopril therapy. Agranulocytosis also developed, and she died of sepsis. A second patient had an initial serum creatinine level of 557 μmol per liter (6.3 mg per dl), and severe facial angioedema developed eight days after he started taking captopril. His facial edema resolved after discontinuation of the captopril. Neither patient had respiratory compromise associated with the angioedema. Singer and MacGregor reported facial angioedema in a patient with moderate renal impairment—serum creatinine level of 318 to 407 μmol per liter (3.6 to 4.6 mg per dl)—after treatment with both captopril and enalapril.[16] There was no respiratory compromise, and symptoms resolved after the ACE inhibitor was discontinued. Gannon and Eby reported angioedema involving the tongue and supraglottic structures shortly after enalapril therapy was started in a patient with end-stage renal failure. The serum creatinine level was not reported, but manufacturer recommendations include a 50% reduction in the initial dose of enalapril in patients with severe renal impairment. This patient did not have an adjustment in the enalapril dose, and this may have contributed to the development of angioedema.

A reduction in the initial dose of lisinopril in patients

with renal impairment is also outlined in the manufacturer's package insert. Patients with a creatinine clearance of less than 0.5 ml per second should begin with a daily dose of 5 mg. Although lisinopril is removed during dialysis, in patients receiving dialysis, the recommended initial dosage is 2.5 mg daily.

The mechanism of ACE inhibitor-associated angioedema has undergone extensive evaluation. It is probably related to bradykinin potentiation by the ACE inhibitors. The kinins have multiple effects and are probably mediators for a variety of cutaneous reactions, including urticaria, angioedema, flushing, and pruritic reactions. Bradykinin is metabolized by two kininases, I and II. Kininase II is actually angiotensin-converting enzyme, and ACE inhibitors will inhibit kininase II to increase bradykinin levels.[1] Increases in bradykinin levels following ACE inhibitor administration have been reported in both animals and humans.[2]

It is attractive to implicate an increase in bradykinin levels after ACE inhibitor administration as the mechanism behind the development of angioedema. Atlas and co-workers, however, were unable to show an increase in bradykinin blood levels after administering ACE inhibitors.[18] Others have demonstrated increases in the cutaneous wheal response after administering intradermal bradykinin in patients receiving enalapril.[19,20] Ferner and colleagues also noted flushing associated with the administration of intradermal bradykinin, suggesting the systemic absorption of bradykinin.[20] This would imply decreased local metabolism of bradykinin during ACE-inhibitor therapy. An increase in the histamine dermal flare response was also shown in patients receiving captopril.[21] This reaction is associated with kinin release, and the reaction was most evident at higher doses of captopril. When the effect of a single 25-mg dose of captopril on intradermal skin testing to histamine, codeine, and bradykinin was evaluated in ten normal volunteers, the wheal-and-flare reaction to bradykinin was found to be increased significantly after captopril administration, with a less consistent response to codeine and no significant change to histamine.[22] Half of the volunteers also had flushing after the bradykinin skin test. The sum of these investigations strongly supports the hypothesis of ACE-inhibitor potentiation of bradykinin as the mechanism behind the development of angioedema in these patients.

Although angioedema associated with the use of ACE inhibitors is generally considered an idiosyncratic reaction, its severity may be accentuated in patients with renal insufficiency. There is substantial drug accumulation in these patients. Because increased bradykinin levels appear to be the mechanism behind ACE-inhibitor–associated angioedema, it is reasonable to speculate that patients with renal insufficiency would also have increased levels of bradykinin. This would translate into more severe episodes of angioedema and may explain the higher incidence of severe angioedema that we have observed with lisinopril use. The overall incidence of angioedema associated with lisinopril use may be similar to that with other ACE inhibitors, but the longer half-life and potency of lisinopril may predispose to more severe episodes of angioedema, especially in patients with renal impairment.

Patients 1 and 2 had compromised renal function that probably contributed to the accumulation of lisinopril and the development of severe angioedema. Both had creatinine clearances of less than 0.5 ml per second (calculated based on age, weight, and serum creatinine level), and lisinopril therapy had been initiated at a higher than recommended dose (10 mg) based on the creatinine clearance. Although patients 3 and 4 had only minimally elevated serum creatinine levels, the estimated creatinine clearance was 0.7 and 0.65 ml per second (44 and 39 ml per minute), respectively. The lisinopril dosage was increased from 10 to 30 mg daily in patient 3 during his hospital course, and he probably had considerable lisinopril accumulation as a result of his reduced creatinine clearance. Patient 4 also had reduced renal function.

In patients 3 and 4, the initial presentation of respiratory distress was not attributed to lisinopril. Both patients received additional doses of lisinopril after the initial occurrence of respiratory distress and angioedema. In patient 3, the concomitant administration of prednisone probably masked his adverse reaction to lisinopril, which became evident only after the prednisone dose was tapered. Patient 4 presented with a moderate reaction to lisinopril that was originally attributed to his nasal spray. He received an additional dose of lisinopril, which probably precipitated the onset of stridor and the need for ventilatory support.

In summary, impaired renal function and the continued administration of lisinopril after the initial adverse reaction are two explanations for the higher-than-expected incidence of severe angioedema in our series. Alternatively, lisinopril use may be associated with an increased incidence of severe angioedema because of its greater potency. This was not recognized in the initial clinical evaluation of lisinopril and may be an adverse reaction that becomes evident only after extensive use. Although none of our patients died, all four had life-threatening reactions. This underscores the need for close monitoring of these patients, proper dosing, and the prompt discontinuation of the medication after the development of angioedema. Because angioedema can be considered a class effect, subsequent antihypertensive therapy in these patients should be with another class of agents.

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Commentary

Bedside Teaching

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The place of bedside teaching and physical diagnosis in modern medicine is problematic. A number of surveys have suggested that patients like case presentation and discussion at the bedside very much[1-4] but that students, house staff, and faculty do not.[5-9] Tremonti and Biddle, using direct observation, found that the median time spent at the bedside was only 2.5 minutes, compared with 69 minutes in the classroom.[5]

Reasons given for not wanting to be at the bedside include fears and discomfiture of the patient—evidently not justified by objective data—and, perhaps a ruling reason, fears of the house staff, students, and attending physicians of being "exposed" as imperfect in the presence of a patient. This "loss of face," though not overtly expressed by most of those surveyed, is, I think, preeminent. Other problems with bedside rounds include the fact that one has to stand up, there is a lack of access to blackboards, x-ray films, and the like, and, depending on how it is done, it may be boring for students and house staff not directly involved in the immediate demonstration or elicitation of findings.

The problem will get worse if the data accumulated by Wang-Cheng and colleagues are correct: though 85% of patients preferred bedside rounds, only 35% of attending physicians did so (with younger attending physicians favoring "remote rounds"); only 4% of students and 2% of house staff—who will presumably carry these attitudes with them when they become teachers—preferred bedside rounds to remote rounds.[9]

The argument for bedside rounds is that they put patients right back in the center of the attention of physicians, as opposed to making them almost incidental to the laboratory data, x-ray film reports, and theoretic discussions of the pathophysiology of disease. Bedside rounds, therefore, are the most patient-centered of all teaching venues. It is also true that if we cast our minds back to the most memorable parts of our teaching experience as students and house officers, they are most likely to involve particular patients rather than lectures in a conference room. If endurance in memory is any indication of the valuable aspects of medical education, then by removing ourselves from the bedside, we are removing ourselves and our students from the most vivid and dramatic stage on which learning can occur. The phenomenon of the decline in bedside rounds also seems to be mirrored in a declination of time spent at the bedside during work rounds, where, in one study, house staff spent a median of 9 minutes per patient at the bedside versus 32 minutes on work rounds doing other things.[5]

At a time when the American Board of Internal Medicine and the public are both emphasizing the need for interpersonal skills, teachers of medicine appear to be removing themselves from the only site in all of medical education where such skills can be demonstrated. It would be intuitively likely that such central parts of a physician's craft as the illumination of history, the integration of history, physical, and laboratory results, and the therapeutic interpersonal skills of a physician would be more effectively transmitted by demonstration than by lecture. The farther away from the bedside we go, the less opportunity our students have to observe experienced clinicians exercising their skills in the diagnostic and therapeutic relationship with patients. Only at the bedside can such skills be taught.

Physical diagnostic skills are clearly on the decline among American house officers. Although the value of history is not doubted by most physicians, internists see the physical examination as being less valuable than laboratory and radiologic studies.[10,11] This may lead our students to a rude shock when they begin to practice. In a survey published in 1988, graduates of internal medicine training programs who were ten years out rated the skills they thought to be most important in practice. The respondents listed history taking, physical examination, and the judicious selection of diagnostic tests as paramount and thought that their programs had overprepared them in clinical procedure skills and underprepared them in clinical practice skills, including history taking, physical examination, and the judicious use of diagnostic tests.[12]

For all of these reasons, a renewed emphasis on bedside rounds seems not only appropriate but urgent. How shall we, then, conduct bedside rounds to answer the fears and resistance of our house staff, faculty, and students and lessen any discomfiture, even though it be small, that patients may experience?

Before the Bedside

The attending physician or a designated house officer or student should prepare the patients for bedside rounds

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by informing them, as much as possible, of exactly what is going to happen. It may happen that the house officer or student most familiar with the patient has cogent reasons for not wishing to present the case at the bedside. These reasons would include paranoid ideation on the part of the patient, a possible delusional misperception of the likely conversation, extreme anxiety, or patient refusal. The attending physician must evaluate the reasons with care because events in a patient's history that embarrass the house staff may not be embarrassing to the patient and may be specious reasons not to make bedside rounds. When one of my house officers did not want to do bedside rounds because the patient used intravenous cocaine, the reasonable question to her was, "Does not the patient know this?" In Wang-Cheng's study, only a few patients were embarrassed by discussion in their presence, but 88% voiced strong opposition to hallway discussion because of concerns about breaching of confidential information.[9] Most patients to whom I have spoken are less concerned about what their roommates might hear—so long as the patient hears it also—than they are about the unknown listeners in the hall.

Before going to the bedside it is important that the attending physician reassure the house staff and students that he or she will avoid in any way "uncloaking" their ignorance or inexperience and by warning them that it is possible that the attending physician will discern something they have not—which is the purpose, in part, of the exercise. I tell my house staff and students that this is because they have done the yeoman labor of acquiring the immense amount of information that goes into their presentation, allowing me the leisure to explore areas yet unexplored by them. It is also important for the attending physician to be ready to teach something of value. Not knowing what the history is until the bedside case is presented means this requires certain degrees of talent and agility. Even if attending physicians are less skilled in the particular area of expertise required for the illumination of a patient's case, they may demonstrate interpersonal skills in interacting with the patient, emphasizing again the essential role of bedside rounds in this most important part of our craft.

There will, of course, be occasions when cases may be presented in the hall, physical examination done at the bedside, and further discussions occur in the conference room. In most instances, however, all of these can occur entirely at the bedside if the attending physician is unafraid.

At the Bedside

Interacting with the patient is paramount, including properly introducing and identifying the attending physician. If, for example, the attending physician is a teaching attending and not the primary responsible physician, then clarification of that point to the patient is essential. Other skills that may be taught at the bedside, even without expertise with the particular disorder presented, include observation, historical inquiry, and the demonstration of physical skills at the bedside. A good way to integrate laboratory and physical diagnosis, whenever a nonphysical diagnostic study has shown a finding that could have been determined by physical examination but was not, is to try to correlate the results of that study with the findings of the physical examination. Because the history now often contains major laboratory diagnostic findings of previous admissions or physician visits, the attending physician is given a rich opportunity to seek, during the physical examination, confirmation or denial of the reliability of the nonphysical diagnostic study. For example, should it be reported during the history that the computed tomographic (CT) scan of the brain taken in the emergency department showed a lesion, the attending physician could try to determine if neurologic findings are present that correspond to the lesion seen on CT scan. If the echocardiogram has shown tricuspid insufficiency, the attending physician can demonstrate the physical maneuvers necessary to bring out the salient murmur. In this way, confidence in the accuracy of both physical and nonphysical studies may be tested. One may similarly try to predict from the physical examination the results of nonphysical diagnostic studies. For this reason, at bedside rounds, I have house officers give the history and physical findings but not the laboratory results obtained after admission. I will then ask myself, the students, or the house officers not involved in the direct care of the patient to predict the hematocrit or the bilirubin level, predicated on the physical examination findings.

Most important, before leaving the bedside, solicit questions from the patient about what has just happened. It is also valuable to send the house officer or student involved back in to see the patient within an hour or two to again ask if there are any questions.

After the Bedside

At this point one may clarify, consolidate, and integrate the information and expand into the theoretic abstract instead of the immediate concrete. Do not be afraid to go back with the entire team to solicit further history or physical examination findings, if you discover in your discussion that they have been omitted. I also find this time of value to make assignments to the house staff, students, and to myself. These assignments include questions to be asked of the medical literature, with a report to the team the next day, further history from other sources such as family or previous physicians or a major review of the underlying biochemistry or pathophysiology of the disorder discussed. These assignments then precede bedside rounds on the next day. This is also an appropriate time to survey the house staff and students to find out how things went at the bedside and to seek their suggestions to improve the next exercise.

As with all teaching, it is work.

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* * *

AT THE POINT OF DEATH IN ROOM 631

His blood pressure eases in retreating waves.
The patient imagines his God lifting a finger
away from a network of tubes in his chest, easily,
like a small boy at a seaside, letting his moat drain.
What was there, that has left?

Thoughts prickle his scalp, almost caressing.
Shaky breathing begins under a flat sternum,
like a weak pump without a prime.
His fingers are like thirsty beaches, waiting for blood.
His ears push away sound.

Pressure. It was through him, his whole life.
He sees it like a cliff he has tumbled over,
head first into a loose motion wash,
like an ocean, running over a dune.
He licks saltless sweat.

God *is* pressure, he believes, as
drops form on his forehead, too neat,
like speckled death pearls, varied spheres,
oyster white shells. Pinpoints of form,
born from a void of white forehead.

There is a rush toward paleness.
Lips lord over it justly, frankly, like royal amethyst.
Dark eyes begin to retreat under lids.
With so many miles of capillaries in his hands,
rivulets, widening, he has been loosed,
and pressure floats over the land of the body.

SARAH COLLINGS©
Milford, Connecticut

Radiologic Case

Buttock Abscess and Abnormal Findings on Chest X-ray Film

MICHAEL C. PETERSON, MD, *Salt Lake City, Utah*

A "Radiologic Case" is published in this format on a regular basis. Physicians interested in contributing to the series are encouraged to send their radiologic cases to the series' editor.

JONATHAN M. LEVY, MD
Series' Editor

A 35-year-old homeless man presented with low back pain and a football-sized abscess of the right buttock. The abscess was drained, and cultures were negative for pathogens. Six weeks later, the patient returned with pain in the right leg. He was found to have weakness and impaired sensation in the right leg and a new left lower quadrant mass. A leukocyte count was 7.2×10^9 cells per liter (7,200 per μl) with 0.01 bands, 0.55 neutrophils, and 0.34 lymphocytes. A routine chest film (Figure 1) and computed tomographic (CT) scan of the abdomen (Figure 2) were done.

What is the most likely diagnosis in this patient?

How would you confirm the diagnosis?

What other test would you do?

How would you treat this patient?

SEE FOLLOWING PAGE FOR DIAGNOSIS AND DISCUSSION

Figure 1.—A posteroanterior chest film shows tiny nodular opacities of the left lung and pleural fluid with possible pleural thickening in the left base.

Figure 2.—Computed tomography of the abdomen shows a large psoas abscess.

(Peterson MC: Buttock abscess and abnormal findings on chest x-ray film. West J Med 1993 Apr; 158:421-422)

From the Department of Medicine, LDS Hospital, Salt Lake City, Utah.
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ANSWER: Disseminated tuberculosis

THE CHEST FILM in this patient shows a micronodular infiltrate in the left lung, with fluid or pleural thickening (or both) in the left base. This pattern can be caused by a host of inflammatory conditions and occasionally by a malignant neoplasm. The CT scan shows a large mass of fluid density in the left psoas muscle. A magnetic resonance scan of the lumbar spine was also done and shows extension of the inflammatory process into the L-4 and L-5 vertebral bodies and into the sacrum with an associated spinal epidural abscess (Figure 3). The association of a pulmonary infiltrate with a psoas abscess should prompt a strong suspicion of tuberculosis as the etiologic agent. Acid-fast bacilli cultures of specimens of the abscess drainage and induced sputum were positive for *Mycobacterium tuberculosis*.

Historically, the incidence of tuberculosis in the United States steadily decreased before the emergence of human immunodeficiency virus (HIV) infection. Since the onset of the acquired immunodeficiency syndrome epidemic, the disease has reappeared, and the number of people affected has grown steadily over the past five years. There has also been an increase in cases of drug-resistant tuberculosis and of infection with atypical organisms. Extrapulmonary involvement and atypical pulmonary manifestations are more common in immunosuppressed patients. Testing for HIV should certainly be considered for any patient found to have tuberculosis.

Back pain is the most common presenting complaint in patients with spinal tuberculosis.[1,2] This may be associated with either a psoas abscess or a paraspinal inflammatory mass.[1,2] *Mycobacterium tuberculosis* has been reported as the causative organism in 10% to 30% of epidural abscesses.[3,4] Leukocytosis is not present in most of these cases,[3] nor does a negative skin test rule out tuberculosis.[1,2,4,5] Culture of the inflammatory material establishes the diagnosis.

Figure 3.—Magnetic resonance imaging of the spine shows erosion of the L-4 and L-5 vertebral bodies and of the sacrum as well as a spinal epidural abscess.

This patient underwent surgical drainage of the psoas abscess and was started on a four-drug antituberculous regimen—isoniazid, rifampin, pyrazinamide, and ethambutol hydrochloride. Patients have been successfully treated with antituberculous agents alone and with surgical drainage followed by drug therapy.[2] Percutaneous CT-guided drainage might also be used for the treatment of psoas abscess, when the process is localized.

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Editorials

Cholesterol Awareness—Key to Preventing Coronary Artery Disease

ALTHOUGH THE ROLE OF hypercholesterolemia in the causation of coronary artery disease (CAD) was once a highly controversial issue, it is now generally accepted by both lay and professional groups that high plasma cholesterol levels contribute substantially to CAD risk. A vast number of epidemiologic studies and both basic and experimental studies in animals support this concept. Importantly, many intervention studies in humans have now convincingly shown that lowering plasma cholesterol levels prevents the progression of CAD and possibly even causes regression. Conceptually, the "Cholesterol Controversy" is over in this country,[1] and attention is now being focused on such important practical issues as, at what level of plasma cholesterol should intervention be initiated? which patients should be treated with aggressive hypolipidemic agents? and what should be the goals of cholesterol lowering in such patients?

Atherosclerosis is a complex and multifactorial disease that involves the reactions of the arterial wall to elevated low-density lipoprotein (LDL) levels and various circulating blood elements and cells.[2] A key to understanding this concept is that hypercholesterolemia, from a pathophysiologic point of view, probably occurs whenever the plasma cholesterol level exceeds 4.15 mmol per liter (160 mg per dl). There is a continuum of increasing risk for complications of atherosclerosis as plasma cholesterol levels exceed this level. Although it may be true that there would be little, if any, CAD if plasma cholesterol levels were lowered to less than 4.15 mmol per liter, it is not likely that this will occur any time soon. Furthermore, there is great variability in the clinical expression of CAD for any given level of cholesterol above this one. Even patients with familial hypercholesterolemia who have had a lifelong elevation of cholesterol differ considerably in the age at which their CAD becomes manifest. For this reason, much effort is being directed at understanding the mechanisms involved in atherogenesis and, in particular, the role that LDL plays in this process. For example, it now seems likely that modifications of LDL, such as oxidative modification, play an important, if not obligatory, role in mediating the atherogenicity of the LDL particle.[3] If this recently developed hypothesis is correct, the atherogenicity of LDL may be determined not only by its levels in plasma, but by the degree to which the LDL particle is modified in the artery wall. Furthermore, this hypothesis implies that inhibiting the modification process, such as by using antioxidant therapy to prevent LDL oxidation, should inhibit atherogenesis independently of lowering LDL levels.

While this hypothesis will likely undergo clinical trials designed to test its validity in the near future—do antioxidants prevent CAD?—it should not be forgotten that lowering plasma LDL levels is an effective way to reduce the number of LDL particles potentially available for further modification. Effective therapies for lowering LDL levels in most persons are currently available.[4] As noted earlier, data are already at hand documenting that lowering LDL levels prevents the atherogenic process, even if we do not fully understand the mechanisms by which this occurs. There are currently many "traditional" risk factors, such as smoking, hypertension, and the presence of diabetes mellitus, that independently increase the risk for CAD. Although new risk factors such as Lp(a), small dense LDL particles, and hyperinsulinemia, are being described, until future research teaches us how to use these factors to define persons at risk for any given level of cholesterol, we are left with the empiric observation that within reason, "the lower the cholesterol, the better." This is particularly true for patients at high risk because of a strong family history, the presence of additional risk factors, or known CAD. For them, the goal of therapy should be to reduce total cholesterol levels to 4.15 mmol per liter (160 mg per dl) and LDL-cholesterol levels to below 2.60 mmol per liter (100 mg per dl).

The recognition that lowering the plasma cholesterol level can be effective in both primary and secondary prevention has led to programs designed to educate physicians and the public on the need to measure cholesterol levels in all adults. In 1988, the National Cholesterol Education Program (NCEP) published guidelines for the screening and evaluation of hypercholesterolemia (*Arch Intern Med* 1988; 148:36-69). The NCEP guidelines have been widely disseminated. In their interesting report, Walsh and colleagues document that in a university-based general internal medicine practice, these guidelines were being followed to a remarkable degree.[5] Of the eligible patients, 80% had been screened. The guidelines of the NCEP had been prominently displayed throughout the clinic, and physicians appeared to follow them. Although university-based physicians might be expected to be more in concert with the latest recommendations, other data also suggest that the intense campaign to educate all physicians about the need to measure cholesterol levels is having a major effect. Schucker and coworkers reported that in 1990 more than 90% of physicians reported the awareness and use of the recommendations of the NCEP.[6] Recent data from Frank and associates suggest substantial increases in cholesterol-related knowledge and behavior and lower plasma cholesterol levels among the general population as well.[7]

The important message is that once a consensus has been reached by responsible physician leadership, as occurred in 1985 with the Cholesterol Consensus Conference,[8] concerted national campaigns, such as the NCEP and the American Medical Association's Campaign Against Cholesterol, can profoundly influence the behavior of physicians and public alike. Knowledge gained from basic research and clinical trials has led to an

improved understanding of the need to control plasma cholesterol levels, and this information is now being translated into preventive measures that can be expected to substantially affect the future expression of CAD. The NCEP guidelines are currently being revised to accommodate the new information that has recently accumulated. This information will undoubtedly be disseminated rapidly and effectively, and appropriate campaigns to achieve this goal are needed. Studies such as that done by Walsh and colleagues are important in helping to assess the effectiveness of such campaigns. Similarly, as new therapies emerge from ongoing basic and clinical research, effective strategies to disseminate the new information need to be developed in parallel. Educating physicians and the public is a vital link in the process of improving the public health.

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Therapies Directed Against Endotoxin—Has the Time Come?

In the United States alone, more than 200,000 deaths each year are attributed to sepsis and septic shock.[1] Chemotherapy, transplantation, invasive procedures, and the acquired immunodeficiency syndrome epidemic have increased the number of immunodeficient patients who are at risk for septic shock. Newer antibiotics and intensive care technologies have been helpful in the management of patients with this disease, but death rates have changed little in the past 20 years. Therefore, additional therapies are needed to prevent and treat life-threatening manifestations of septic shock. The development of new treatments, however, may depend on defining how and when this syndrome occurs and what factors influence its outcome.

Our understanding of pathophysiologic events associated with septic shock has improved in recent years, though much remains to be learned. Septic shock appears to result from complex interactions among bacterial toxins, bacterial virulence factors, host inflammatory responses, and physiologic dysfunction of multiple host organ systems.[2] Some of these interactions are not detrimental to the patient, but rather protect the patient against bacterial invasion and ultimately prevent severe organ injury and death. Given the complexity of this syndrome, pharmaceutic companies should be commended for investing in therapies that might improve mortality or decrease the incidence of sepsis. The enthusiasm that welcomes these therapies, however, should not prevent a critical analysis of all in vitro, animal, and clinical studies. In this issue of The Western Journal of Medicine, Fang presents a timely review of the use of monoclonal antibodies against endotoxin, an investigational therapy for gram-negative sepsis.[3]

The concept that therapies directed against endotoxin, a constituent of gram-negative bacteria, might protect against morbidity from gram-negative infection is the consequence of more than 60 years of research. Fang provides an extensive review of studies examining the ability of the administration of endotoxin to mediate many of the pathophysiologic events of sepsis. In animals and humans, administering endotoxin produces organ dysfunction and cytokine release like those associated with bacterial sepsis.[4] These data suggest that endotoxin may be a fundamental mediator of septic shock and that antiendotoxin therapies might improve the outcome of this syndrome. Fang counterbalances this enthusiasm with data from the use of gram-positive bacteria that show that these pathophysiologic events can occur without endotoxin or endotoxemia.[5] Thus, the presence of endotoxin is sufficient, but not necessary, to produce septic shock. These results also suggest that antiendotoxin therapies would not be beneficial in all cases of septic shock.

Fang discusses the study of Danner and co-workers, who measured circulating endotoxin levels in patients with septic shock to determine whether endotoxemia correlated with the clinical results.[6] As stated in the review, results showed that endotoxemia was present in 43% of patients with septic shock and when present was associated with more severe manifestations of the disease. An additional finding of this study, however, was that the quantitative level of endotoxemia did not correlate with measures of severity of illness. Thus, endotoxemia was a marker of severe septic shock, but its level did not predict outcome. This finding raises some doubt as to whether a therapy that reduces the circulating level of endotoxin would be able to improve the outcome for patients with septic shock.

Despite the uncertain relationship between endotoxin levels and pathophysiologic events in septic shock, endotoxin-directed antibody therapy has been enthusiastically pursued by several investigators over the past two decades. Antibody therapies have been directed at the phylogenetically conserved inner core region of endotoxin, because these antibodies may cross-protect against diverse gram-negative bacteria. One such antibody, E5, a murine immunoglobulin (Ig) M monoclonal antibody, was found to prevent the effects of endotoxin challenge in

sheep and to protect mice administered live bacteria. Subsequently, in a large placebo-controlled trial of patients with signs of gram-negative sepsis, administering E5 did not affect the overall mortality but increased survival in a retrospectively defined subgroup of patients without refractory shock.[7] A second large clinical trial of the use of E5 failed to confirm the results of the first trial, although complete results of this second clinical trial have not yet been published.

Another antibody, HA-1A, a human IgM monoclonal antibody, was initially reported to bind to endotoxin and various gram-negative bacteria. Initial studies showed that administering HA-1A protected rabbits against the endotoxin-induced dermal Shwartzman reaction and increased the survival of mice given lethal doses of gram-negative bacteremia. After these preclinical studies, the use of HA-1A underwent a large, randomized, placebo-controlled trial in patients with presumed gram-negative sepsis. Like that with E5, HA-1A therapy did not affect the overall survival rate, but, based on a revised analytic plan, investigators reported that its use improved the 28-day survival rate in the subgroup of patients with gram-negative bacteremia and shock. United States Food and Drug Administration reviewers rejected this revised plan when they discovered that the original plan had been amended after interim results had been examined.[8] The revision contained the 28-day time point for survival analysis, which was not part of the original plan. Analysis of the study according to the original prospective analytic plan showed no notable effect of HA-1A use on survival. Therefore, the therapeutic efficacy of HA-1A has not yet been proved. A second large, multicenter clinical trial of HA-1A therapy in sepsis is currently under way.

Since the results of the HA-1A trial were published, many controversies have emerged about data from preclinical studies of this agent. Some investigators have reported that HA-1A binds to a wide variety of antigens, gram-positive bacteria, fungi, lipids, and constituents of endothelial cells.[9] Others have been unable to reproduce studies showing a protective effect of HA-1A in animals.[10] Moreover, in a recent investigation using a canine model of gram-negative septic shock, we found that administering HA-1A actually increased mortality.[11] In this randomized, blind, placebo-controlled trial, dogs were infected with an intraperitoneal clot containing *Escherichia coli* and treated with cardiovascular support, antibiotics, and either HA-1A or placebo (a control human IgM or human serum albumin). We found that the use of HA-1A (compared with placebo) was associated with a more severe form of septic shock syndrome, manifested by a worsened hemodynamic state and worsened organ dysfunction. In addition, administering HA-1A did not alter endotoxemia or bacteremia. These results suggest that its use has the potential to produce harmful effects in animals with gram-negative septic shock.

Scientists at Centocor, Inc (Malvern, Pa), the manufacturer of HA-1A, have attempted to explain the difficulty in reproducing results from murine and rabbit studies of HA-1A. Their data suggest that HA-1A binds to endotoxin and fixes complement, that HA-1A–endotoxin-complement complexes are cleared from the circulation by binding to complement receptor 1, and that these complexes are cleared through erythrocytes.[12] Because complement 1 receptors are present on the erythrocytes only of humans and nonhuman primates, the implication is that relevant studies of HA-1A can be done only in primates. Not all nonprimate studies of HA-1A have shown a lack of effect, however; specifically, our canine study showed a harmful effect. Even if the complement 1-receptor mechanism for HA-1A were validated, the possibility cannot be excluded that the effects of HA-1A seen in septic dogs might also apply to some human infections.

There is at this time no scientific proof that mandates the use of any therapy directed against endotoxin in human septic shock. Antibodies against the core region of endotoxin have not demonstrated significant survival benefit in several large multicenter clinical trials.[7,13,14] These circumstances demonstrate that our basic understanding of new therapeutic opportunities in septic shock is still incomplete. The question of whether endotoxin is truly an appropriate target for the treatment of gram-negative septic shock remains unresolved.

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Use of Antiplatelet Agents in the Management of Thrombotic Disorders

In western societies, coronary and cerebral atherosclerotic vascular disease is the major cause of morbidity and mortality.[1] Patients who have symptomatic atherosclerotic disease, such as transient ischemic attacks or unstable angina, or patients who have recently survived a stroke or myocardial infarction, as well as those with documented atherosclerotic peripheral arterial disease, are known to be at an increased risk of subsequent stroke, myocardial infarction, and death caused by cardiovascular disease. Clinical trials carried out during the past 20 years have shown that inhibiting platelet function with the administration of aspirin or ticlopidine hydrochloride reduces the incidence of thrombo-occlusive and thromboembolic complications of atherosclerotic arterial vascular disease and prosthetic cardiovascular devices.[2-5]

In this issue of the journal, Goodnight and colleagues discuss the indications, agents, and recommended regimens that achieve effective antiplatelet therapies.[6] Their review summarizes a large number of published controversial information that is complicated by large multicenter trials of varying quality in design, execution, and analysis. Because the trial results were often inconclusive and sometimes contradictory, meta-analyses have been useful in resolving controversial therapeutic recommendations. The evaluation by Goodnight and co-workers is notable on two accounts. First, it includes brief descriptions of important recent trials, thereby conveying an appreciation for the complexity inherent in these large studies, including occasional confounding outcomes. Second, the recommendations for therapy reflect a broad understanding and objective evaluation of many relevant trials.

As discussed by Goodnight and colleagues, the most complete and reliable overall evaluation of therapeutic benefits and recommendations arising from antiplatelet trials comes from the recent reports by the Antiplatelet Trialists' Collaboration.[7,8] This group, coordinated through Oxford and Edinburgh, has now analyzed more than 200 randomized trials involving more than 100,000 patients. On the basis of their meta-analysis, the researchers conclude that antiplatelet therapy is efficacious in reducing the frequency of the composite outcome of stroke, myocardial infarction, or death due to cardiovascular disease in patients at increased risk of such events, irrespective of their specific clinical presentations. An additional important published source identified by Goodnight and associates regarding practical recommendations for antiplatelet therapies is an updated article published last year in *Chest*.[9] On the basis of this substantial body of evidence, Goodnight and co-workers recommend specific antiplatelet therapeutic regimens that reliably reduce the incidence of thrombo-occlusive and thromboembolic complications for all major arterial beds—that is, the cerebral, coronary artery, and peripheral vascular distributions. The protection is achieved irrespective of the anatomic site producing the initial presenting symptoms. Three additional recommendations deserve emphasis:

- The evidence is not convincing that the primary prevention of vascular events with aspirin therapy is indicated in the general population. This conclusion is based on the results of two studies evaluating the primary prevention of vascular events with the use of aspirin among American[10,11] and British[12] physicians. Although both studies showed a reduction in the incidence of nonfatal myocardial infarction, they also showed some increased incidence of disabling stroke and no net reduction in the number of deaths due to cardiovascular disease. These findings do not justify administering aspirin to a large number of asymptomatic persons for prolonged periods.
- Antiplatelet agents also improve the patency of aortocoronary-saphenous vein or internal mammary artery bypass grafts by approximately 30%.[13,14] For example, aspirin given at a moderate dosage (325 mg) produces benefits equivalent to higher doses (325 mg three times a day), and the addition of dipyridamole to higher-dose aspirin therapy fails to increase the effect over the use of aspirin alone. Moreover, initiating aspirin therapy (325 mg per day) six hours after an operation retains aspirin's antithrombotic effects without the increased risk of operative bleeding associated with aspirin therapy started preoperatively. Thus, patients undergoing saphenous vein or internal mammary artery-aortocoronary grafting should receive a regimen of aspirin (325 mg per day) initiated early after the operation and continued for at least one year.
- In addition, low-dose aspirin therapy (100 mg per day) prevents systemic embolism and death from cardiovascular disease in patients with mechanical valve replacement or high-risk tissue valve replacement treated with warfarin sodium (international normalized ratio 3.0 to 4.5). The addition of a low dose of aspirin to warfarin therapy reduces mortality, death due to cardiovascular disease, and the incidence of major embolism, with some acceptable increase in the incidence of hemorrhage.[15]

In summary, there is good evidence that aspirin therapy is of benefit in patients with atherosclerotic disease who are at high risk of vascular events and that the beneficial effects of aspirin are similar in men and women, patients with and without diabetes mellitus, old and young. There is no persuasive evidence that the combination of dipyridamole and aspirin is any better than the use of aspirin alone, and sulfinpyrazone is not as effective as aspirin. Ticlopidine use is probably more effective than aspirin therapy in patients at risk of vascular events. Both aspirin and ticlopidine have adverse effects, however (aspirin primarily produces dose-dependent gastrointestinal side effects; ticlopidine causes reversible dose-independent neutropenia in about 1% of patients and dose-limiting diarrhea in about 10% of patients).

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Correspondence

Unconventional Therapy

To the Editor: I would like to thank Dr Lewis for proving once and for all that unconventional therapy is the method of choice in patients with advanced cancer.[1] I am certain that this was not his intent, but in quoting the study by Cassileth and colleagues, this is precisely what he has done. His article states that in matched patients with advanced cancer, half of whom were treated at a large university medical center and half of whom were treated at a clinic that administered unconventional therapy, the survival time was comparable. In other words, state of the art oncology at a large university medical center was unable to provide a better survival rate than a clinic providing unconventional therapy. In light of the mammoth costs associated with the large medical center and because the survival rate is comparable, why would anyone opt for the expensive oncologic therapy at the university when the results will be the same at a clinic using unconventional therapy?

If I am to take the responsible approach to addressing the problem of unproven therapies, as Dr Lewis suggests, what should I tell my patients—that for those with advanced cancer, unconventional therapy is just as effective as conventional therapy?

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Dr Lewis Responds

To the Editor: The Cassileth study cited by Dr Taylor and me was designed to compare the outcome of patients with far-advanced cancer cared for at a large academic medical center with those treated at the Livingston-Wheeler Clinic, San Diego, California.[1] The patients had advanced, refractory colon or rectal cancer, malignant melanoma, or unresectable adenocarcinoma of the pancreas. The study predicted the survival rate would be similar in both groups, and it was. Medical oncologists seldom affect survival rates in these patients. They can improve the quality of life by addressing complications and assuring the patient and family that the medical management team and various support systems, including hospice, will be available to help.

The treatment used at the Livingston Clinic was an autogenous immune vaccine made against a microorganism, named by Dr Livingston-Wheeler, *Progenitor cryptocides*. The existence of this biologic entity has never been acknowledged by medical science; it is a make-believe microorganism, and thus the patients were being treated with a make-believe "vaccine." Using this "vaccine," the Livingston-Wheeler Clinic claims an 82% success rate with managing cancers.[2,3] The public undoubtedly interprets this to mean that they cure many patients or improve the quality of life of most. Cassileth's study refutes these claims. As mentioned in my commentary, the real lesson of this study was that the quality of life was better among patients cared for at the academic medical center. The patients did not live longer at the Livingston-Wheeler Clinic, and they had a reduced quality of life while under the clinic's care.

Dr Taylor wonders if, because patients did not live longer at the academic institution, unconventional therapy is just as good as standard management and maybe cheaper. Because costs of care were not calculated, assertions about expenses are inappropriate. Indeed, careful management by experienced oncologists may be less costly than management by practitioners who rely on make-believe therapies.

The purpose of my commentary was not to discuss the results of the study but to explore the ethical and human subject review aspects entailed in designing and carrying out a clinical protocol in which one of the arms employed an agent that did not really exist. I continue to think that such a study cannot be ethically carried out under human subject informed consent procedures.

Using therapies that have not been proved effective and that are based more on wishful thinking than solid scientific data is neither ethical, efficacious, nor proven to be economical.

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Health Care Reform—Epidemiology and the Science of the Sustainable

To the Editor: In a recent editorial on health care reform in the United States, Dr Clever articulates a diverse array of characteristics that will have to shape a reformed system.[1] She notes that "science is our particular intellectual underpinning" and refers to care that should range from the preventive through the acute to rehabilitative. As an epidemiologist who works at the preventive and public health end of the spectrum of the health care system, I would argue that to be sustainable, health care reform will require, in addition to these qualities, a fundamental revisioning of the system's orientation, its point of intervention in the causal development of disease, and, ultimately, a significant evolution in our general cultural values with respect to the locus of responsibility for individual health.

The most striking feature of the health care reform debate thus far is its use of economics rather than epidemiology as the sole basic scientific tool for evaluation and planning. Physicians throughout the health care system should recognize the incomplete nature and illogic of our reform debate: there is no basic science. Included among Dr Clever's needed characteristics should be a health care system driven by 21st century patterns in the epidemiology of disease in the United States. Substituting economics for epidemiology as the central science in reshaping health care—that is, addressing only economic issues such as access, coverage, structures for provider payment, insurance overhead—will result in revisiting these same problems in the journal in the year 2002 or shortly thereafter. The crisis in US health care has arisen primarily from the occurrence of disease unchallenged by a coherent national control strategy that is driven by epidemiology and emanates only secondarily from finite or maldistributed health resources. No amount of economic restructuring without the application of epidemiologic principles and data can build in the kind of adaptability needed to keep up with the pace of American demographic, epidemiologic, and economic changes.

Only when epidemiology drives national disease control planning, implementation, and evaluation will the ideal strategy for the distribution and economics of health service delivery become apparent and rational. Using epidemiology in health care reform will draw attention to the fact that a disproportionate amount of health care monies is spent in treating late-stage disease in the last years—and often the final days—of life. Epidemiology will also show that the greatest burden of disease affecting Americans involves voluntary choice and life-style and is largely preventable. Eliminating smoking and reducing alcohol abuse would decrease by more than half the chronic diseases and injuries that annually kill, hospitalize, or disable Americans. An estimated 90% of American cancers are caused by environmental and behavioral choice factors; readily modifiable factors include diet and tobacco use, which are responsible for 35% and 30%, respectively.[2] Injuries kill more Americans aged 1 to 34 than all diseases combined, are the leading cause of death through age 44, and cause more loss of working years of life than all forms of cancer and heart disease combined.[3] Most are readily preventable, yet the United States spends a pittance on research and implementation of injury prevention strategies.

If we wish health care reform to be sustainable, the health care system will have to shift the focus of disease control to earlier in the causal or pathogenic chains of disease. Only through improved prevention, both primary and secondary, will the cost savings be generated to allow excellence in both tertiary hospital care and general public health. In the current system, the former is thriving while the latter is contracting, and the imbalance is everywhere apparent in ill health, poor standing for the United States in international comparisons of health, and decay in the health infrastructure. At a cultural level, Americans will have to stop equating a highly technologic, interventionist, and immediately gratifying approach with good health care. Ultraspecialization does not reflect and should not be equated with medical competence. We have tried this ethos, and, by itself, it cannot work in the face of an aging and increasingly economically polarized society. Furthermore, a health care system cannot be sustained if it creates dependency in the service population and effectively divorces the concept of individual responsibility for healthy choices from actual health status. We will never be able to afford (nor should we want) to intervene therapeutically in the face of any abuse that people willingly inflict on their bodies. These are not simply problems of our health care system, they are examples of dysfunctional thinking within our greater culture. Dr Clever mentions the need to attend to issues that may seem more social than medical, such as drug abuse, guns, and violence, but the social nature of our problems is equally germane to the classical medical conditions that lead as causes of American morbidity and mortality. Indeed, as the great physiologist Rudolph Virchow wrote in 1849,

> Once medicine is established as anthropology . . . the physiologist and the [medical] practitioner will be counted among the elder statesmen who support the social structure. Medicine is a social science in its very bone and marrow.[4]

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Dr Clever Responds

Close reading of my editorial[1] will show that Dr Gellert and I do not disagree substantially. I appreciate his emphasis on epidemiology and prevention as important elements in health care reform. Even monumental population-based data and educational efforts, however, would not relieve physicians' responsibility to care for and comfort those who "willingly inflict [abuse] on their bodies." Compassion is an essential part of health care and health care reform.

LINDA HAWES CLEVER, MD

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Lessons From the Practice

Just One Night for Mr John Doe

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The hospital census rises sharply during the harsh winter months. One patient looms in my memory.

He is found shortly after 10 PM in an abandoned car, and the race against time begins. An emergency service ambulance speeds through the maze of icy streets, building momentum with each passing block. The attendants burst through the clanging emergency department doors.

A tall, middle-aged man lies motionless on the gurney. The odor emanating from his body smells like raw sewage. His face looks like a dirt road too often traveled, with deep grooves, potholes, and a myriad of intersecting lines. His eyes recede deep in their sockets, dull gray like an overcast sky. His matted hair and wiry beard are alive with small black crawling insects.

He is shrouded in a long, ragged, grease-stained trench coat fastened at the top by a large safety pin, the kind used to secure laundry bags. A lamp cord belt cinches his waist. His tattered trousers balloon like ship sails in poor repair. The bottoms of his shoeless feet are as black as any asphalt road and twice as tough. Charcoal-colored hands feel like weather-beaten leather gloves. He is unconscious and hypothermic. The radial pulse is thready and feeble; respirations are rapid and shallow. He feels as cold as ice. Miraculously, he does not suffer severe frostbite. The patient is corpse-like, forgotten, like most of the dead.

We call him John Doe for lack of a better name and admit him immediately to the intensive care unit. We begin the process of resurrecting this blighted soul.

Everything considered, Mr Doe is quite fortunate. The nurses bathe, shave, and feed him like a king. We diagnose and treat a severe bilateral pneumonia. Several days of intensive care improve Mr Doe's outward appearance. Little intrinsic change occurs, however. He hoards food from his tray. His eyes dance furtively like a wild boar in captivity. His communicative repertoire consists of "yes," "no," or a blank, faraway stare.

After ten days of psychiatric consultation, Mr Doe establishes a rapport with a social worker, who discovers that he is a Vietnam veteran from Ohio. Several days later he is transferred to the Veterans Affairs hospital. Mr Doe is fortunate. The number of homeless persons in this country ranges from 250,000 to 3 million. The percentage of mentally ill in the homeless population may be as high as 91%. The loss of labor force and potential is devastating.

Mr Doe is a bona fide medical save. Through a large expenditure of dollars and time, our medical team tricked death on his behalf. In private, we grapple with the consequences of our actions: the prolongation of life versus suffering.

Mr Doe teaches us that the homeless are not simply bums; they are persons who may have complex medical and psychological problems. The need for public, private, medical, and governmental awareness and commitment to the homeless is imperative. The solution to the problem will not be found in just one night but in the dawn of our understanding and resolve.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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Assistant Editors

(Trowers E: Just one night for Mr John Doe. West J Med 1993 Apr; 158:430)

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(Continued from Page 352)

SPONSORS OF COURSES—ABBREVIATIONS

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.

CS: Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.

DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.

FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.

ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.

LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.

LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.

OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.

PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.

UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.

UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.

USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.

UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.

UV: Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 15—**Pharmacologic Management of Dementia.** Bellingham. Thurs. Contact: (206) 676-1712.

April 15-16—**Tacoma Surgical Club.** Tacoma. Fri. Contact: PCMS CME.

April 16—**Cardiac Risk Factors.** Seattle. Fri. Contact: U/W.

April 16—**20th Annual Day of Pediatrics.** Tacoma. Fri. Contact: Multicare. (206) 594-1221.

April 23—**Terminal/Palliative Care Update.** Tacoma. Fri. Contact: PCMS CME.

April 23-24—**Clinical Allergy for the '90s.** Seattle. Fri-Sat. Contact: VMMC.

April 23-25—**Washington State Physical Therapy Association.** Seattle. Fri-Sun. Contact: Children's. (206) 526-2501.

April 28-30—**Emergency Physicians Annual Scientific Assembly.** Seattle. Wed-Fri. Contact: Washington Chapter, American College of Emergency Physicians. (206) 441-9762.

April 30-May 1—**Mental Health.** Seattle. Fri-Sat. Contact: U/W.

April 30-May 2—**Radiology Annual Meeting.** Vancouver, BC. Fri-Sun. Contact: Pacific Northwest Radiological Society. (206) 441-9762.

May 6—**Hematology/Oncology.** Bellingham. Thurs. Contact: (206) 676-1712.

May 6-7—**Aging and the Elderly.** Seattle. Thurs-Fri. Contact: U/W.

May 7—**Disability Prevention in Workers' Compensation: Cumulative Trauma Disorders and Low Back Injuries.** Seattle. Fri. Contact: (206) 956-6817.

May 7—**Office Gynecology.** Tacoma. Fri. Contact: PCMS CME.

May 8—**Stroke Prevention and Management of Cerebral Vascular Ischemia.** Seattle. Sat. Contact: U/W.

May 13—**Cardiology Update.** Everett. Thurs. Contact: Pacific Northwest Medical Education Institute. (206) 258-6322.

May 14-15—**Northwest Spine Review Course.** Seattle. Fri-Sat. Contact: VMMC.

May 15—**Infectious Diseases.** Seattle. Sat. Contact: U/W.

May 17-18—**Introduction to AIDS Clinical Skills for Primary Care Providers.** Seattle. Mon-Tues. Contact: U/W, (206) 720-4250.

May 20—**RX of Glomerulonephritis.** Bellingham. Thurs. Contact: (206) 676-1712.

May 22—**Pain Management for Primary Care Physicians.** Seattle. Sat. Contact: U/W.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

June 3-4—**Travel Medicine.** Seattle. Fri-Sat. Contact: U/W.

June 4-5—**Surviving the Elements.** Seattle. Thurs-Fri. Contact: U/W.

June 19—**Medical Malpractice: Biennial Update.** Seattle. Sat. Contact: U/W.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare. (206) 592-1221.

June 25-26—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

July 9—**Update From the IXth International AIDS Conference in Berlin, Germany.** Seattle. Fri. Contact: U/W.

August 2-7—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

August 27-28—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 13-17—**21st Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

October 22-23—**Adolescent Medicine.** Seattle. Thurs-Fri. Contact: Children's Hospital, (206) 526-2501.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 18-19—**Regional Musculoskeletal Conference.** Seattle. Thurs-Fri. Contact: U/W.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆

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PROGRAM PROFILE

CENTER FOR SKULL BASE SURGERY

A CASE STUDY

A 35-year-old man presented with the acute onset of a severe headache. Diagnostic tests revealed an intracranial aneurysm at the junction of the basilar artery and the anterior inferior cerebellar artery, causing sub-arachnoid hemorrhage. Operative approaches for aneurysms in that area are considered difficult and dangerous.

Nevertheless, surgeons at the Center for Skull Base Surgery used a new technique, combining an approach through the temporal bone with newer microsurgical instrumentation.

The otolaryngologist, Dr. Dennis R. Maceri, first drilled out the mastoid, identifying those structures related to hearing that were to be preserved. Dr. Steven L. Giannotta, neurosurgeon, then dissected the aneurysm and put clips on it to obliterate it. Dr. Maceri finished the procedure by closing the brain covering with a watertight fat graft from the patient's lower abdomen.

The patient has made a full recovery and resumed his normal activities of weight lifting, skiing and flying ultra light aircraft.

Historically, lesions at the base of the skull have represented some of the most difficult challenges in operative neurosurgery. Older techniques at management of tumors or vascular lesions in this region were not satisfactory. The cavernous sinus, in particular, represented a "no man's land" because of the risks associated with direct surgical intervention in this area.

However, recent advances in diagnostic imaging and surgical techniques have allowed direct operative management of skull base lesions to become a reality. The advent of magnetic resonance imaging, sophisticated angiography and a better understanding of surgical micro-anatomy in conjunction with improvements in microsurgical instrumentation have enabled previous "inoperable" lesions to now be excised with acceptable risks.

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'he highly sensitive intracranial area equires the extensive skill and collabrative approach that can only be proided by several specialties, working ı harmony. In 1990, USC University ospital organized a specialized team f internationally renowned surgeons ı the fields of neurosurgery, plastic nd reconstructive surgery, otolaryngology, neuroanesthesia, neuropathology, neurointerventional radiology and euro-ophthalology to work gether as a osely coordiated team. The tegration of this ide range of perts allows the SC University ospital Center r Skull Base rgery to offer a mprehensive, ulti-specialty ogram to mane complicated ull base lesions. ıe Center for ull Base Surgery incorporates the lents of these disciplines under the adership of Director Takanori ıkushima, M.D., D.M.Sc., an ternationally recognized pioneer in skull base surgery and Associate Director William T. Couldwell, M.D., Ph.D., a specialist in brain tumors and tumor biology research.

The USC University Hospital Center for Skull Base Surgery, one of the most comprehensive programs of its kind in the United States, serves as a primary West Coast referral center for intracranial disorders. Members of the interdisciplinary team are committed to maintaining close contact with referring physicians to ensure effective patient management for optimal recovery.

SKULL BASE SURGERY TEAM
Takanori Fukushima, M.D., D.M.Sc., Director
William T. Couldwell, M.D., Ph.D., Assoc. Director
Michael L.J. Apuzzo, M.D.
Steven L. Giannotta, M.D.
Dennis R. Maceri, M.D.
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CALIFORNIA MULTISPECIALTY. Urgent Care Director, Dermatologist, Radiologist, Otorhinolaryngologist, General Surgeon, Cardiologist, Internal Medicine, Pediatrician, Gastroenterologist, Orthopedist, General/Family Practitioner, Obstetrician/Gynecologist. Excellent opportunity for physicians to join 400 member multispecialty medical group serving 42 locations in the greater Los Angeles area and Orange county. Large fee-for-service and prepaid practice, no Medi-Cal. Excellent compensation program based on guarantee plus incentive, profit sharing and pension plan. Group provides health, dental, life, and malpractice. Partnership in real estate and medical corporation available. Send CV to Ron McDaniel, Assistant Administrator, Mullikin Medical Center–5, 17821 S Pioneer Blvd, Artesia, CA 90701.

TACOMA–GIG HARBOR, WASHINGTON shared office and partnership practice for recently trained Internist with an interest in Geriatrics. Excellent remuneration package and call schedule. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411; FAX (415) 399-0411.

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BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

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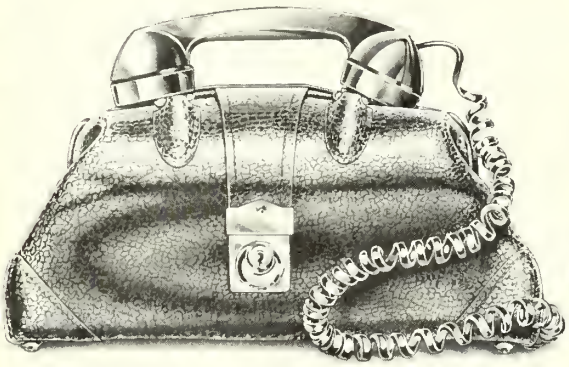

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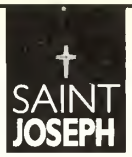

New Mexico

Excellent opportunity for board certified or board eligible OB/GYN, Pediatric, Internal Medicine and Family Practice physicians to practice within MED-NET (Medical Network of New Mexico), an integrated health care system. Enjoy sunshine, skiing, hiking, fishing and hunting in a Southwestern lifestyle. For further information contact Anne Winter, Director of Professional Development, The St. Joseph Healthcare System, Albuquerque, New Mexico.

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FAMILY PHYSICIAN–LEWISTON, IDAHO
Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson; or call (208) 743-8416.

SAN FRANCISCO BAY AREA. Primary Care office practice seeks associate for future partnership. Excellent patient mix, modern office near shopping mall. Collegial medical staff with support from 200-bed community hospital. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411; FAX (415) 399-0411.

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

GENERAL INTERNIST. The VA Medical Center, Long Beach, California is recruiting for a staff physician. Duties include seeing patients in the Walk-In Clinic, the Emergency Room, and supervision and teaching of housestaff in the clinic. The VA is affiliated with the College of Medicine at the University of California, Irvine. Vacancy is full-time position, 40 hours per week, US citizenship is required. Please send CV to David Webb, MD, Associate Chief of Staff, Ambulatory Care (153), VA Medical Center, 5901 E 7th St, Long Beach, CA 90822. The VA is an equal opportunity employer.

PHYSICIANS WANTED

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

OCCUPATIONAL MEDICINE. Opportunities available in northern and southern California for highly qualified physicians for positions available at Occupational Medicine facilities. Two years experience is preferred, but will train highly qualified applicants with less experience. Attractive compensation and scheduling. Excellent working environment in top quality facilities. Please contact Ron D'Acchioli, Administrator, at (310) 829-8214 or FAX résumé to (310) 829-8270.

EMERGENCY MEDICINE–FAMILY PRACTICE. California Emergency Physicians Medical Group (CEP) is a physician partnership which currently staffs 29 Emergency Departments and seven Ambulatory Care Centers throughout California. Opportunities available for physicians BC/BP in Emergency Medicine, Family Practice, Internal Medicine, and/or experienced in Primary Care. CEP offers stable contracts, excellent compensation, profit sharing, as well as health, disability, and retirement programs. For immediate consideration send CV or contact John Gravette, CEP, 2101 Webster St, #1050, Oakland, CA 94612; (800) 842-2619.

(Continued on Page 438)

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(Continued from Page 437)

PHYSICIANS WANTED

PRIMARY CARE IN THE PACIFIC NORTHWEST Diverse opportunities for Family Physicians in urban and rural health centers throughout Washington, Oregon, Idaho, and Alaska. Loan repayment possible. Practice where it's nearly perfect. Send CV to Sarena Seifer, MD, Northwest Regional Primary Care Association, 4154 California Ave, SW, #7, Seattle, WA 98116; (206) 932-2133.

HAWAII. FAMILY PRACTITIONER WITH OB SKILLS and Internal Medicine physician needed for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Puanani Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792. (808) 696-7081.

ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

OPPORTUNITY. BC physician (Family Practice, Internal Medicine, or Occupational Medicine) for a busy private/industrial medicine practice in Los Angeles. Bilingual preferred (medical Spanish required). Clinic is affiliated with a major medical center. Excellent salary. Send CV to Number 281, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SALT LAKE CITY–URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

PHYSICIANS WANTED

INTERNAL MEDICINE/PRIMARY CARE. BC/BE, recently trained (university program preferred) for group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

NEVADA–GASTROENTEROLOGIST. BC/BE needed to join Gastroenterology practice in southern Nevada. Generous salary leading to full partnership. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

CALIFORNIA. NONINVASIVE CARDIOLOGIST needed to join an invasive established Cardiologist. 8:00-5:00 office practice only. Short drive from San Diego and Los Angeles. Competitive salary and benefits. Send CV or call Anil Rastogi, MD, 2390 E Florida Ave, Hemet, CA 92544; (909) 652-5555.

EXCELLENT OPPORTUNITY FOR INTERNAL MEDICINE PHYSICIAN in private practice multispecialty physician group in San Francisco. Income guarantee. No investment. Forward CV to Box 263, The Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved, needed to join clinics in Milton-Freewater, and Hermiston, Oregon. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

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CONTACT with CV to: **Nancy Chaffins**

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(509) 482-2164
FAX: (509) 482-2187

ENJOY THE GREAT SOUTHWEST. Thomas-Davis Medical Centers, an expanding multispecialty group of 190 plus physicians, needs BC/BE Pediatrics, Internal Medicine, Family Practice, OB/GYN, Urgent Care, Urology, General Surgery, Psychiatry, and Hematology/Oncology physicians. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. Call or write TDMC/CPR, (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

INTERNIST/FAMILY PRACTICE. Physicians for well loved multidisciplinary Geriatric health center. Part of east San Francisco bay area community clinic network. Permanent and locum tenens positions available. 50-80% time. Participation in hospital and call coverage desired. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

FAMILY PRACTICE. Seeking Family Practice or General Practice physician for rapidly growing area in northern Arizona – Bullhead City, Arizona/Laughlin, Nevada. Opportunity unlimited. Compensation unlimited. Malpractice and health insurance. Send CV to Bullhead Medical Center, 1648 Highway 95, Bullhead City, AZ 86442, or FAX to (602) 763-1311.

ATTENTION PHYSICIANS. Find the right physician for your practice by placing a classified advertisement. Call WJM for more information; (415) 882-3376.

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PHYSICIANS WANTED

MIDWEST

Due to steady major light industry expansion, there are several opportunities for BC/BE Family Physicians in the lakes region of Northeastern Indiana. Affiliated with a hospital that had operating revenues of $20 million last year. Weekly clinics: Orthopedics, Neurology, Gastroenterology, Pulmonology, Cardiology, Urology, and Oncology all seeing 10% growth last year. Modern, full service, waterfront hospital located 25 miles from a major city. This facility has the second largest home health care department in the state which exceeded 100,000 home health care visits last year. Enjoy many rural and urban activities and access to nearby universities. Excellent income guaranteed and $20,000 sign-on bonus, all benefits, and overhead. Call 1:6. **Call Cheryl Broderick at (800) 762-9213.**

EXPANDING INDUSTRIAL MEDICAL CLINIC. Physician wanted for San Francisco location. Full-time, Monday through Friday. Excellent compensation plus malpractice insurance. Send CV to The Branch Office, Box 238, 842 Folsom St, San Francisco, CA 94107.

SOUTHWEST. Established, quality BC Family Practitioner seeks associate. OB optional. Significant Occupational Medicine component to practice. Beautiful office near 350 plus-bed tertiary facility. Third fastest growing city in US with sunshine an average of 355 days per year. Perfect climate for all outdoor recreation, including swimming, exploration of mountain trails, and watching minor league sports teams. Home of several colleges and universities, the area also hosts international and local cultural activities for the whole family. Population 600,000, service area 3 million. Salary plus bonus and benefits. Contact Cheryl Broderick at E.G. Todd Physician Search; (800) 762-9213.

FLORIDA GULF COAST. Two BC Hematologists/Oncologists seeking third to join pure subspecialty practice. Competitive salary and excellent benefits. ECOG, GOG. Sophisticated medical community with a tropical climate. Send CV with cover letter to Practice Manager, 306 South Blvd, Ste B, Tampa, FL 33606.

THERE'S GREEN IN YOUR FUTURE. Thomas-Davis Medical Centers, Arizona's largest and most successful multispecialty group, needs an experienced BC/BE Internist or Med/Ped to join two others at its clinic in beautiful Green Valley, Arizona. Green Valley is located only 26 miles south of metropolitan Tucson. The retirement community of Green Valley offers picturesque views, suburban lifestyle, five golf courses, and shopping in Mexico. Top benefits, profit sharing, guarantee first two years plus incentive pay, early shareholder, and signing bonus. Call or wnte Dee Pones, (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732. FAX (602) 322-2676.

THE VA MEDICAL CENTER, PRESCOTT, ARIZONA is seeking a BC/BE Internist with or without subspecialty. Regular hours. Experience with Holter monitors, treadmill testing, and/or endoscopy desirable but not necessary. Prescott is a lovely area with beautiful surroundings, clean air, pleasant lifestyle, wonderful dry four season climate. Interested physicians may call (602) 445-4860, ext 6640, or send CV to Robert Parsons, MD, Acting Chief, Medical Service, VA Medical Center, Prescott, AZ 86313. An equal opportunity employer.

(Continued on Page 440)

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Arizona: CIGNA Healthplan of AZ, Physician Recruitment, 11001 N. Black Canyon Hwy, Suite 400-49, Phoenix, AZ 85029, (800) 252-2471.

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(Continued from Page 439)

PHYSICIANS WANTED

FAMILY PRACTICE. Premier multispecialty group near Portland, Oregon has two excellent opportunities for BC/BE Family Practitioners. Join one of two satellite clinics in which Family Physicians and Physician Assistants currently practice. Superb lifestyle, abundant recreational opportunities, and generous benefits package. Send CV to Karen Stanton, c/o The Vancouver Clinic, 700 NE 87th Ave, Vancouver, WA 98664.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

TWO INVASIVE CARDIOLOGISTS AND FAMILY PHYSICIANS NEEDED. Unique opportunity. Gorgeous California central coast. Partnership within year. Send references/CV to PO Box 220, 395 Del Monte Center, Monterey, CA 93940.

PHYSICIANS WANTED

PHYSICIAN, MEDICAL DIRECTOR

Idaho's Department of Health and Welfare, State Hospital North, has an opportunity for a physician as Medical Director for a 75-bed adult substance abuse and Psychiatric treatment hospital. Primary responsibilities include patient medical diagnosis and treatment; medical consultation; shared on-call; employee wellness and infection control. Small facility allows for progressive and innovative practice and a participative management style. Competitive salary; relocation assistance; excellent benefit package. Rural setting located at the base of the Selway-Bitterroot Wildemess Area. Experience Idaho – it's what America used to be! Contact Marvin Lambrecht, Administrator, State Hospital North, PO Box 672, Orofino, ID 83544; (208) 476-4511.

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SAN FRANCISCO BAY AREA–PEDIATRICIAN. Recently trained, energetic, enthusiastic, BC preferred, for 18 physician Palo Alto Medical Clinic satellite. Clinic is progressive 150 physician multispecialty group known for innovation and excellence. Practice is established and growing. Excellent location, convenient access to San Francisco and Stanford Excellent compensation/benefits package. Please send CV and letter of interest to David Hooper, MD, Medical Director, Palo Alto Medical Foundation, 39500 Liberty St, Fremont, CA 94538.

PHYSICIANS WANTED

MEDICAL DIRECTOR/CLINICIAN

Family Practice, OB optional, opening July 1, 1993 for Berkeley Primary Care community clinic. Competitive salary, paid professional liability insurance, reasonable call requirements. Spacious, modern, fully equipped office. Accessible to the beautiful San Francisco bay area.

PLEASE CONTACT:

John Ford, MD
Berkeley Primary Care Access Clinic
PO Box 11406
Berkeley, CA 94701-2406
(510) 204-4624 or (510) 204-4536

INTERNAL MEDICINE–Southern California. Challenging career opportunities for specialists in Internal Medicine desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels. 2600 Cliff Dr, Newport Beach, CA 92663.

PUGET SOUND–WASHINGTON STATE. RHEUMATOLOGY independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

PRIMARY CARE PHYSICIAN to join comprehensive health care team focused on prevention. This multidisciplinary model utilizes Day Health Centers and Home Support to keep frail elderly participants in the community active and maximally independent. Opportunity for innovation and for collaborative research with 15 similar programs. Please contact Marc Sapir, MD, The Center for Elders Independence, 1411 E 31st St, Ward B2, Oakland, CA 94602; (510) 436-7702.

URGENT CARE/PRIMARY CARE PHYSICIANS. Current permanent positions available in Phoenix, Denver, Colorado Springs. Attractive settings with reasonable workload. Enticing locum tenens assignments available also throughout the Rocky Mountain west. Call or write Ed Novelli, Interim Physicians, 4155 E Jewell, Ste 1018, Denver, CO 80222; (800) 669-0718.

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Maurice Montag in care of Tammie Johnson, 8009 S 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

PUGET SOUND–WASHINGTON STATE. ENT independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

NEPHROLOGIST WANTS PARTNER/ASSOCIATE BC/BE Gastroenterologist/Cardiologist/Nephrologist/Pulmonologist. Excellent practice, equal partnership opportunity without buy-in or overhead. Send CV to Dr M. Streger, 27800 Medical Center Rd, Ste 122, Mission Viejo, CA 92691.

PUGET SOUND–WASHINGTON STATE. OB/GYN independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

(Continued on Page 441)

(Continued from Page 440)

PHYSICIANS WANTED

MARKS MEDICAL PLACEMENTS
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NEONATOLOGIST needed to provide medical care to sick/premature infants in level III/high level II nurseries within Neonatal Intensive Care Units at institutions within northern two-thirds of Arizona. Responsible for parent communication, family and staff education, completion and maintenance of billing description, and medical records documentation. Will teach/supervise Pediatric, Obstetric, and Family Practice house staff, and Neonatal Nurse Practitioners within Newborn Intensive Care nurseries. Will provide educational activities for community physicians with ten level II institutions with which company has contractual relationships. 40 plus hours per week including 1:4 call nights per week and 1:3 weekends per month. Work schedule varies as appropriate for Neonatal/Perinatal practice. Salary: $150,000 per year. Requirements: MD degree, two years Pediatric residency, one year internship and two years Neonatal fellowship, six years experience in job offered or eight years as practicing Neonatologist, plus certification by American Board of Pediatrics, certification by American SubBoard of Neonatal-Perinatal Medicine, and State of Arizona medical license. (Job location: Phoenix.) Qualified applicants send résumé or application letter with ad by April 30, 1993 to Ann Marie Voss, Administrative Assistant, Neonatology Associates, Ltd, 300 W Clarendon, Ste 375, Phoenix, AZ 85013. Employer paid ad. Proof of authorization to accept permanent full-time employment in the US required if hired.

FAMILY PRACTICE AND INTERNAL MEDICINE, Southern California. Join FHP Health Care, one of America's most successful HMOs. Here's your chance to be part of a Primary Care Delivery System that gives you autonomy to shape your practice and the support of quality healthcare professionals. BC or BE required. Call toll-free (800) 336-2255 or send your CV to FHP Professional Staffing, Dept 45, 9900 Talbert Ave, Fountain Valley, CA 92708. EOE.

PEDIATRICIANS–Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

BC/BE GASTROENTEROLOGIST is needed to join a busy Gastroenterology practice in a rapidly growing community in northern California. Must be trained in therapeutic endoscopy. Excellent salary and generous bonus leading to early partnership. Number 282, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

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PHYSICIANS WANTED

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San Mateo County takes pride in its approach to health care service delivery. With the support of dedicated professionals and technicians, our team of health care managers have been successful in meeting the diverse needs of County residents. We're looking for a physician to fill a unique position within the Health Services Agency.

This position offers challenges and opportunities not found in the traditional role of Health Officer. With the assistance of highly competent administrators, you will oversee the operation of the Public Health Division, ensuring the effective and efficient delivery of programs and services that protect and promote public health and mitigate public health hazards. You will have high visibility in the community and will deal extensively with community physicians, schools, the public, and press. You will also serve as the County's medical consultant for the Health Services Agency's management team which includes the directors of Hospitals & Clinics, Environmental Health, Mental Health, and Aging & Adult Services.

Located about 30 miles south of San Francisco, San Mateo County offers the best of California — temperate climate, clean air, proximity to the ocean — an excellent environment for a family lifestyle. We also provide a highly competitive salary and exceptional benefits.

For a descriptive brochure, call the Human Resources Department at **(415) 363-4343**. To apply, send resume and cover letter to: **Brenda Rutherford, Human Resources Department, 590 Hamilton St., Redwood City, CA 94063.** RESUMES WILL NOT BE ACCEPTED AFTER MAY 7, 1993. EOE.

SAN MATEO COUNTY

OB/GYN, INTERNAL MEDICINE, FAMILY PRACTICE

Strelcheck and Associates, Inc currently represents FAMILY PRACTICE positions in Nebraska, Kansas, Texas, Illinois, and Wisconsin–some near the Minnesota border; INTERNAL MEDICINE positions in Wisconsin and Ohio; OB/GYN positions in southeastern Wisconsin. We would be happy to provide you with further information. Please call toll-free, (800) 243-4353 or send your CV to STRELCHECK AND ASSOCIATES, INC, 10624 N Port Washington Rd, Mequon, WI 53092.

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Strelcheck and Associates, Inc, an extension of our clients' recruiting departments, has positions available in Wisconsin and Michigan. We would be happy to provide you with further information. Please call (800) 243-4353 or send your CV to STRELCHECK AND ASSOCIATES, INC, 10624 N Port Washington Rd, Mequon, WI 53092.

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

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Well established, productive Pulmonary practice available. Heart of America–Kansas. Single tertiary hospital and office practice. 1992 net $350,000 plus. **Contact Dan L. Robison; (316) 268-8538, FAX (316) 268-8694.**

MONTEREY BAY. Midway between Santa Cruz and Monterey, this unpretentious community is perfect for the hiker, biker, surfer, and outdoorsperson. Medical staff is anxious to welcome additional BC/BE physicians in Family Practice and Pediatrics. Group and independent practice with call schedule which allows time for lifestyle. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411; FAX (415) 399-0411.

OB/GYN–Southern California. Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

(Continued on Page 442)

Moving Ahead in '93

The California Department of Corrections has a number of opportunities available in the following areas:

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Staff Psychiatrist - Vacaville, San Luis Obispo, Madera, Soledad / Monterey, Corcoran, Wasco, Solano, San Diego, Tehachapi, Tracy, Lancaster, Stockton, Ione, Chino, Frontera, Pelican Bay, Folsom

PHYSICIANS

Internal Medicine - Primary Care - General Practice - Madera, Folsom, Ione, Crescent City, Wasco, Corcoran, Frontera, Norco, Folsom, Vacaville, Calipatria, Lancaster

Positions are flexible: full-time, part-time and contract consultant.
Competitive Salary - Excellent Benefits

For any of the above opportunities, call **(916) 327-7081.**
Or send CV to: John Zil, M.D., J.D., Chief Psychiatrist,
California Department of Corrections
Dept. DHCS, P.O. Box 942883, Sacramento, CA 94283-0001.
Fax **(916) 322-5864** EOE.

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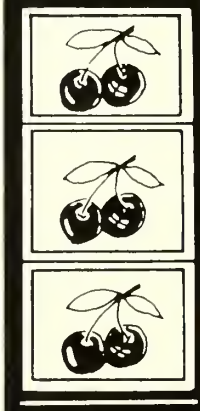

CLASSIFIED INFO (415) 882-3376

(Continued from Page 441)

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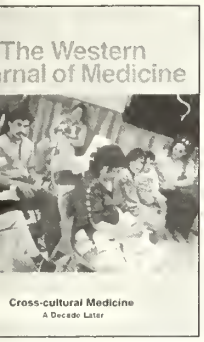

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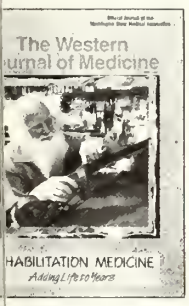

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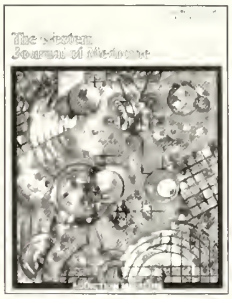

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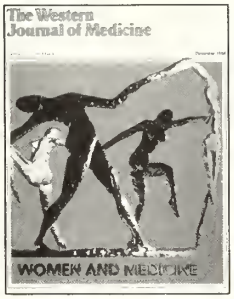

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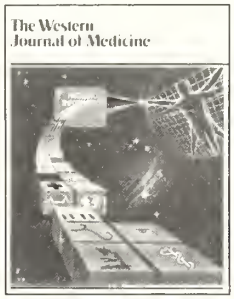

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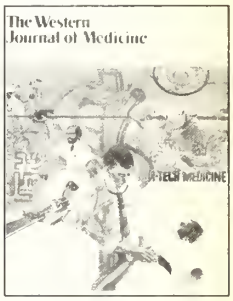

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol* 1991;14:146-151.

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient appnsed of the potential hazard to the tetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clotibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life ($t_{1/2}$) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin.* See WARNINGS: Skeletal Muscle.

Antipyrine. Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol. Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin. In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine. The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin. In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SQ 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area (mg/meter^2). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug:

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3*	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interections.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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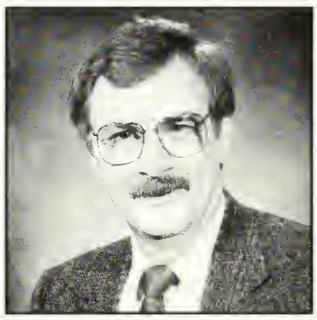

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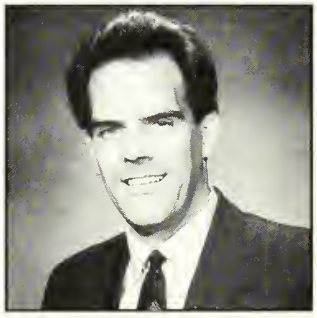

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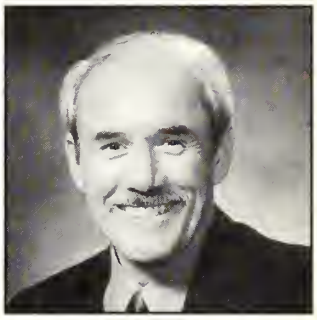

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ntraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or -degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory ass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

rnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection tion < 30%) or moderate to severe symptoms of cardiac failure and in patients with any ree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure h optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally duce hypotension. Elevations of liver enzymes have been reported. Several cases have been nonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on pamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade duction across the accessory pathway bypassing the AV node, producing a very rapid tricular response or ventricular fibrillation after receiving I.V. verapamil (or digitalis). Because his risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-ree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree k requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. us bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypoten- were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated verapamil.

cautions: Verapamil should be given cautiously to patients with impaired hepatic function (in ere dysfunction use about 30% of the normal dose) or impaired renal function, and patients uld be monitored for abnormal prolongation of the PR interval or other signs of overdosage. apamil may decrease neuromuscular transmission in patients with Duchenne's muscular dys-phy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be essary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. nbined therapy with beta-adrenergic blockers and verapamil may result in additive negative cts on heart rate, atrioventricular conduction and/or cardiac contractility; there have been orts of excessive bradycardia and AV block, including complete heart block. The risks of such nbined therapy may outweigh the benefits. The combination should be used only with caution close monitoring. Decreased metoprolol and propranolol clearance may occur when either g is administered concomitantly with verapamil. A variable effect has been seen with combined of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% ng the first week of therapy, which can result in digitalis toxicity. In patients with hepatic hosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The oxin dose should be reduced when verapamil is given, and the patient carefully monitored. apamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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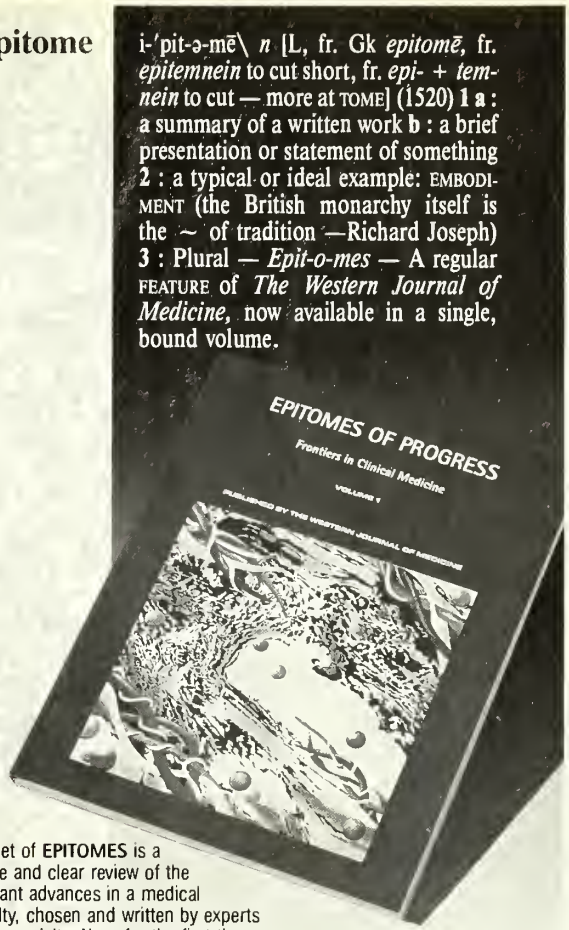
epitome i-'pit-ə-mē\ *n* [L, fr. Gk *epitomē*, fr. *epitemnein* to cut short, fr. *epi-* + *temnein* to cut — more at TOME] (1520) **1 a** : a summary of a written work **b** : a brief presentation or statement of something **2** : a typical or ideal example: EMBODIMENT (the British monarchy itself is the ~ of tradition —Richard Joseph) **3** : Plural — *Epit-o-mes* — A regular FEATURE of *The Western Journal of Medicine,* now available in a single, bound volume.



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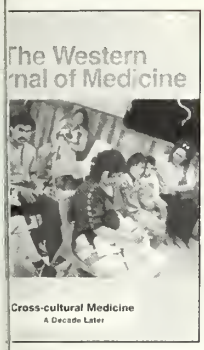

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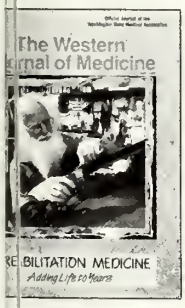

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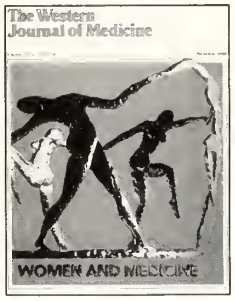

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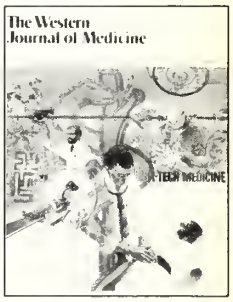

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522 **Acute Dilated Cardiomyopathy as a Cluster in Children**
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From the Departments of Pediatrics and Internal Medicine, Loma Linda University Medical Center, Loma Linda, California.

525 **Cytomegalovirus-Induced Thrombocytopenia in an Immunocompetent Adult**
MARK J. EISENBERG, MD, MPH, and BARUCH KAPLAN, MD

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DEBORAH S. PORTERFIELD

Ms Porterfield is a medical student at the University of California, San Francisco, School of Medicine.

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A source of strength in a world of resistance

CEFOBID® 1g/2g q12h

(cefoperazone sodium) IM/IV

Please see adjacent page for brief summary of prescribing information.

CEFOBID® (cefoperazone sodium) has maintained in vitro activity over time

- An excellent *in vitro* susceptibility profile against the most common nosocomial pathogens[1-3]

Pseudomonas aeruginosa[2,3]		*Staphylococcus aureus*[2,3]	
1985	1990	1985	1990
91.0%	93.1%	92.0%	91.3%
(n=388)	(n=15,439)	(n=369)	(n=2,554)

From a retrospective, multicenter susceptibility data base; n=number of isolates; percent susceptible calculated with 95% confidence limits.

In vitro activity does not necessarily imply a correlation with *in vivo* results.

- An established record of clinical effectiveness in nosocomial pneumonia,* in complicated UTI,* and for approved indications in the febrile neutropenic patient*[4-8]
- No dosage adjustment required for the renally impaired
- Low sodium load
- Convenient, cost-effective q12h dosing

Contraindicated in patients with known allergy to the cephalosporin class of antibiotics

CEFOBID® 1g/2g q12h (cefoperazone sodium) IM/IV

A force against resistance

*Due to susceptible strains of indicated organisms, such as *P aeruginosa*.

References. 1. Horan T, Culver D, Jarvis W et al. Pathogens causing nosocomial infections: preliminary data from the National Nosocomial Infections Surveillance System. *Antimicrobic Newsletter* 1988;5(9):65-67. **2.** Data available on request from Roerig. **3.** Jenkins SG. Comparative susceptibility patterns of common clinical isolates to cefoperazone: 1981 to 1987. *Am J Med* 1988;85(suppl 1A):52-55. **4.** Mangi RJ, Greco T, Ryan J, Thorton G, Andriole VT. Cefoperazone versus combination antibiotic therapy of hospital acquired pneumonia. *Am J Med* 1988;84:68-74. **5.** Mangi RJ, Ryan J, Berenson C et al. Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. *Am J Med* 1988;85(suppl 1A):44-48. **6.** Mangi R, Peccerillo K, Moleski RJ. Treatment of nosocomial pneumonia. Presented as an educational exhibit at the 47th Annual Meeting of the American Society of Hospital Pharmacists, June 3-7, 1990, Boston, Mass. **7.** Cohen MS, Washton HE, Barranco SF. Multicenter clinical trial of cefoperazone sodium in the United States. *Am J Med* 1984;77:35-41. **8.** Kiehl A, Greenberg RN. Treatment of febrile neutropenic patients: evaluation of antibiotic regimens with or without vancomycin. Presented at the 24th Annual ASHP Midyear Clinical Meeting, December 3-7, 1989, Atlanta, Ga.

Brief Summary

CEFOBID® (cefoperazone sodium) *For Intravenous or Intramuscular Use*

CONTRAINDICATIONS: CEFOBID (cefoperazone sodium) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics. **WARNINGS**: BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH THE USE OF CEPHALOSPORINS (AND OTHER BROAD-SPECTRUM ANTIBIOTICS). THEREFORE, IT IS IMPORTANT TO CONSIDER ITS DIAGNOSIS IN PATIENTS WHO DEVELOP DIARRHEA IN ASSOCIATION WITH ANTIBIOTIC USE. **PRECAUTIONS**: Although transient elevations of the BUN and serum creatinine have been observed, CEFOBID alone does not appear to cause significant nephrotoxicity. However, concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity.

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID is increased 2-4 fold in patients with hepatic disease and/or biliary obstruction. In general, total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored.

Because renal excretion is not the main route of elimination of CEFOBID, patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

The half life of CEFOBID is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period. In patients with both hepatic dysfunction and significant renal disease, CEFOBID dosage should not exceed 1-2 g daily without close monitoring of serum concentrations.

As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFOBID. Those at risk include patients with a poor nutritional status, malabsorption states (e.g., cystic fibrosis), alcoholism, and patients on prolonged hyperalimentation regimens (administered either intravenously or via a nasogastric tube). Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.

A disulfiram-like reaction characterized by flushing, sweating, headache and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFOBID® (cefoperazone sodium) administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID. A similar reaction has been reported with other cephalosporins.

Prolonged use of CEFOBID may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.

CEFOBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. **Drug Laboratory Test Interactions**: A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range, the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown. **Usage in Pregnancy, Pregnancy Category B**: Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Usage in Nursing Mothers**: Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman. **Pediatric Use**: Safety and effectiveness in children have not been established. For information concerning testicular changes in prepubertal rats see Carcinogenesis, Mutagenesis, Impairment of Fertility. **ADVERSE REACTIONS**: In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID® (cefoperazone sodium) therapy or uncertain etiology. **Hypersensitivity**: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin. **Hematology**: As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10. **Hepatic**: Of 1285 patients treated with cefoperazone in clinical trials one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms of nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pretreatment levels and the symptomatology resolved. As with other antibiotics that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5-10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established. **Gastrointestinal**: Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibiotic therapy (see WARNINGS). **Renal Function Tests**: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted. **Local Reactions**: CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

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ABSTRACTS MAY 1993

(Murphy EL, Varney KF, Miyasaki NT, et al: Human T-lymphotropic virus type I seroprevalence among Japanese Americans. West J Med 1993 May; 158:480-483)

The epidemiology of human T-lymphotropic virus type I (HTLV-I) infection is not well defined in Japanese Americans. This impairs using approaches that could reduce viral transmission and monitor carriers for the disease. Using enzyme-linked immunosorbent assay and p21e recombinant Western blot testing, HTLV-I antibody was measured in unlinked samples from Japanese-American patients at 4 physicians' offices in San Francisco, California. Of 442 patients, 4 (0.9%; 95% confidence interval 0.25%, 2.3%) were confirmed seropositive, all with an HTLV-I rather than an HTLV-II pattern on Western blot. Seroprevalence was highest among the issei or immigrant generation (3/230 or 1.3%) compared with the second-generation nisei (1/191 or 0.5%) or third-generation sansei (0 of 17). Prevalence did not differ by age or sex, although the number of positive subjects in each subgroup was small. Of 88 patients with familial origins in endemic areas of southern Japan, none were seropositive. In this sample of Japanese Americans, HTLV-I seroprevalence was lower than in residents of endemic southern Japan but higher than among American blood donors. The prevalence was most similar to that in nonendemic areas of Japan. The public health implications of HTLV-I infection among Japanese Americans are discussed.

HTLV-I SEROPREVALENCE
JAPANESE AMERICANS
HTLV-I EPIDEMIOLOGY

(Murphy EL, Varney KF, Miyasaki NT, et al: Human T-lymphotropic virus type I seroprevalence among Japanese Americans. West J Med 1993 May; 158:480-483)

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HTLV-I EPIDEMIOLOGY

(Murphy EL, Varney KF, Miyasaki NT, et al: Human T-lymphotropic virus type I seroprevalence among Japanese Americans. West J Med 1993 May; 158:480-483)

The epidemiology of human T-lymphotropic virus type I (HTLV-I) infection is not well defined in Japanese Americans. This impairs using approaches that could reduce viral transmission and monitor carriers for the disease. Using enzyme-linked immunosorbent assay and p21e recombinant Western blot testing, HTLV-I antibody was measured in unlinked samples from Japanese-American patients at 4 physicians' offices in San Francisco, California. Of 442 patients, 4 (0.9%; 95% confidence interval 0.25%, 2.3%) were confirmed seropositive, all with an HTLV-I rather than an HTLV-II pattern on Western blot. Seroprevalence was highest among the issei or immigrant generation (3/230 or 1.3%) compared with the second-generation nisei (1/191 or 0.5%) or third-generation sansei (0 of 17). Prevalence did not differ by age or sex, although the number of positive subjects in each subgroup was small. Of 88 patients with familial origins in endemic areas of southern Japan, none were seropositive. In this sample of Japanese Americans, HTLV-I seroprevalence was lower than in residents of endemic southern Japan but higher than among American blood donors. The prevalence was most similar to that in nonendemic areas of Japan. The public health implications of HTLV-I infection among Japanese Americans are discussed.

HTLV-I SEROPREVALENCE
JAPANESE AMERICANS
HTLV-I EPIDEMIOLOGY

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In Memoriam

California Medical Association

BERGMAN, SCOTT MALCOLM, Rancho Mirage. Died Dec 29, 1992, aged 36. Graduate of Chicago Medical School, Chicago, Illinois, 1983. Licensed in California in 1987. Dr Bergman was a member of the Riverside Medical Association.

BICKERTON, JOHN H., Jr, La Jolla. Died Dec 17, 1992, aged 81. Graduate of University of Southern California, Los Angeles, 1946. Licensed in California in 1946. Dr Bickerton was a member of the San Diego County Medical Society.

COVER, WILLIAM L., San Bernardino. Died Jan 11, 1993, aged 84. Graduate of Harvard Medical School, Boston, Massachusetts, 1935. Licensed in California in 1938. Dr Cover was a member of the San Bernardino County Medical Society.

CRILE, D. MICHAEL, Hemet. Died Jan 15, 1993, aged 72. Graduate of University of California, San Francisco, School of Medicine, 1946. Licensed in California in 1947. Dr Crile was a member of the Riverside County Medical Association.

DRITZ, H. FRED, San Francisco. Died Jan 13, 1993, aged 73. Graduate of University of Illinois College of Medicine, Chicago, 1944. Licensed in California in 1944. Dr Dritz was a member of the San Francisco Medical Society.

EPSTEIN, FREDERICK M., El Cerrito. Died Feb 9, 1993, aged 76. Graduate of University of Louisville School of Medicine, Louisville, Kentucky, 1942. Licensed in California in 1948. Dr Epstein was a member of the Alameda-Contra Costa Medical Association.

FOBES, CLARK D., Upland. Died Oct 20, 1992, aged 64. Graduate of University of Nebraska College of Medicine, Omaha, 1953. Licensed in California in 1965. Dr Fobes was a member of the San Bernardino County Medical Society.

GILBERT, ALFRED EDMUND, Napa. Died Jan 25, 1993, aged 89. Graduate of Loma Linda University School of Medicine, Loma Linda, California, 1930. Licensed in California in 1939. Dr Gilbert was a member of the Napa County Medical Society.

HEFFERNAN, JAMES J., Jr, Stockton. Died Feb 28, 1993, aged 81. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1937. Licensed in California in 1938. Dr Heffernan was a member of the San Joaquin County Medical Society.

HUNNICUTT, ARTHUR J., Oakland. Died Mar 3, 1993, aged 86. Graduate of Stanford University School of Medicine, Stanford, California, 1935. Licensed in California in 1935. Dr Hunnicutt was a member of the Alameda-Contra Costa Medical Association.

KATZEFF, JACOB, San Bernardino. Died Feb 2, 1993, aged 86. Graduate of Washington University School of Medicine, St Louis, Missouri, 1935. Licensed in California in 1961. Dr Katzeff was a member of the San Bernardino County Medical Society.

KEEFE, ROBERT J., San Francisco. Died Jan 25, 1993, aged 71. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1953. Licensed in California in 1954. Dr Keefe was a member of the San Francisco Medical Society.

LAMB, PHILIP V., Sonora. Died Mar 15, 1993, aged 87. Graduate of University of California, San Francisco, School of Medicine, 1933. Licensed in California in 1933. Dr Lamb was a member of the San Joaquin County Medical Society.

LAMMEL, HARRY G., Vallejo. Died Oct 26, 1992, aged 78. Graduate of University of Nebraska College of Medicine, Omaha, 1942. Licensed in California in 1946. Dr Lammel was a member of the Solano County Medical Society.

MCDONALD, RICHARD H., Huntington Beach. Died Feb 14, 1993, aged 69. Graduate of Johns Hopkins University School of Medicine, Baltimore, Maryland, 1947. Licensed in California in 1955. Dr McDonald was a member of the Orange County Medical Association.

MESSENGER, DAVID L., Placentia. Died Jan 26, 1993, aged 69. Graduate of University of California College of Medicine, Irvine, 1962. Licensed in California in 1975. Dr Messenger was a member of the Orange County Medical Association.

WRIGHT, RICHARD D., San Francisco. Died Nov 1992, aged 52. Graduate of Creighton University School of Medicine, Omaha, Nebraska, 1964. Licensed in California in 1964. Dr Wright was a member of the San Francisco Medical Society.

New Mexico Medical Society

MACQUIGG, RODGER E., Albuquerque. Died Feb 3, 1993, aged 80. Graduate of Ohio State University College of Medicine, Columbus, 1940. Licensed in New Mexico in 1948. Dr MacQuigg was a member of the Greater Albuquerque Medical Association.

ORTEGA, JUAN B., Las Vegas. Died Feb 5, 1993, aged 49. Graduate of University of San Carlos, Guatemala City, Mexico, 1970. Licensed in New Mexico in 1991. Dr Ortega was a member of the San Miguel County Medical Society.

PERRY, STEPHEN R., Farmington. Died Dec 14, 1992, aged 50. Graduate of University of Tennessee College of Medicine, Memphis, 1968. Licensed in New Mexico in 1991. Dr Perry was a member of the San Juan County Medical Society.

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1. US Dept of Agriculture. *Composition of Foods: Pork Products*, 1992. Agricultural handbook 8-10.
2. US Dept of Agriculture. *Composition of Foods: Poultry Products*, 1979. Agricultural handbook 8-5.

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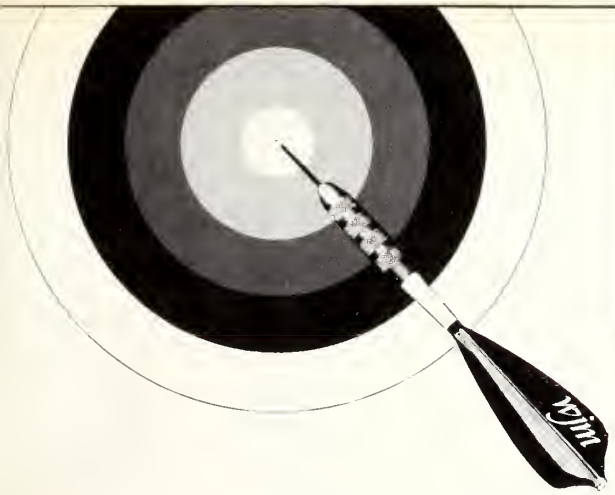

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References:

1. A. Morales et al., New England Journal of Medicine: 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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ABSTRACTS MAY 1993

(Lam KS: Treatment of B-cell lymphoma using peptides—A novel concept. West J Med 1993 May; 158:475-479)

Combination chemotherapy remains the major current treatment of non-Hodgkin's lymphoma. B-cell lymphoma often has tumor-specific surface immunoglobulins called idiotypes. Clinical trials using murine monoclonal anti-idiotype antibodies as a targeting approach have shown some success. I describe a novel concept of using idiotype-specific peptides as an alternative targeting approach for the treatment of B-cell lymphoma. In brief, octapeptides that bind to the surface idiotype of the B-cell lymphoma are isolated from a large synthetic peptide library (10^6 to 10^7 peptides). Once the sequence of a tumor-specific octapeptide ligand is defined, large quantities can be synthesized and conjugated with a radionuclide (such as iodine 131). This should permit highly specific destruction of lymphoma cells that bind the labeled peptide. The theoretic advantages of this approach over the previous use of anti-idiotype antibodies are addressed.

NON-HODGKIN'S LYMPHOMA
B-CELL LYMPHOMA
PEPTIDE THERAPY
IDIOTYPE-SPECIFIC PEPTIDE

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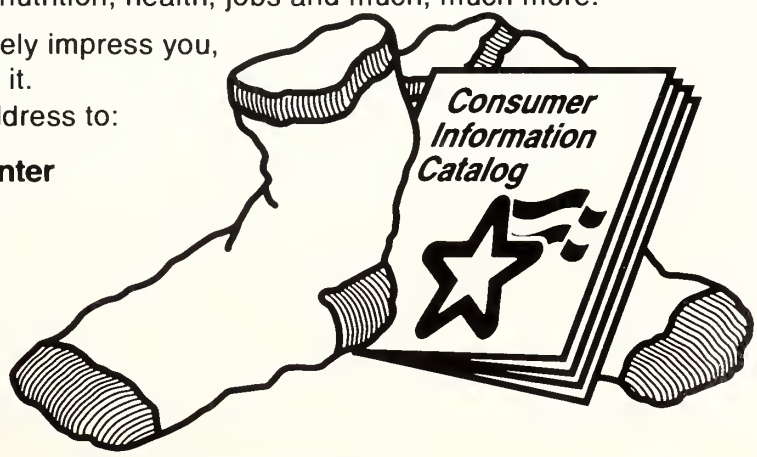

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From the Division of Oncology, Department of Medicine, Stanford University Medical Center, Stanford University School of Medicine, Palo Alto, California.

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From the Primary Care Division, Department of Medicine, Santa Clara Valley Medical Center, San Jose, California.

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Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Since the duration of action of dihydrocodeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

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Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

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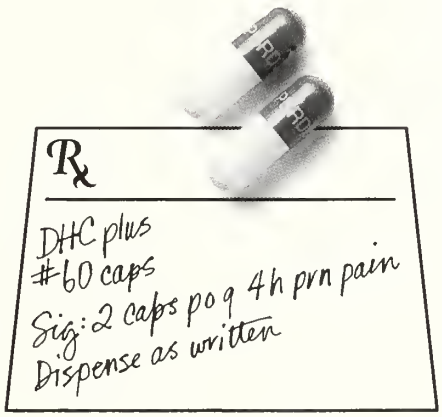

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All references should be medical, scientific, or scholarly publications. Others—newspapers, magazines, etc—should be kept to a minimum and included in the text.

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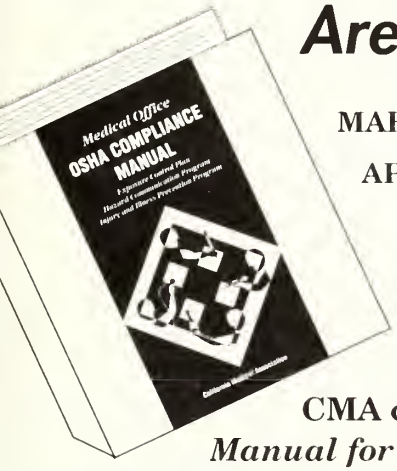

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ALLERGY/IMMUNOLOGY

September 30-October 2—**1st International Conference on Engineered Vaccines for Cancer and AIDS.** St Francis Memorial Hospital and Northern California Melanoma Center at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

ANESTHESIOLOGY

May 20-23—**Annual Meeting of the California Society of Anesthesiologists.** California Society of Anesthesiologists at Monterey Conference Center. Thurs-Sun. 20 hrs. $200. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

May 23-28—**Anesthesiology Review Course.** UCSD at San Diego Princess. Sun-Fri. 45 hrs. $500. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690 (415) 541-0900.

CPMC: California Pacific Medical Center
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DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114 (415) 723-5594.

UCD. University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI University of California, Irvine
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UCLA University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024 (310) 825-8423.

UCSD University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

September 11-12—**Case Conference in Anesthesia.** California Society of Anesthesiology at Hyatt Hotel, Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $195. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

October 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Four Seasons Hotel, Wailea, Maui, Hawaii. Sun-Sat. 23 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

CARDIOLOGY

July 18-22—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. Contact: UCD.

August 5-7—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 16 hrs. Contact: UCSF.

October 1-3—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 14-16—**Cardiology Update: 1993.** UCSF at Quail Lodge Resort and Conference Center, Carmel. Thurs-Sat. 12 hrs. $445. Contact: UCSF.

CARDIOVASCULAR DISEASE

June 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marriott Hotel, Monterey. Fri-Sun. 12 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 25-27—**Preventive Cardiovascular Medicine: Challenge for the '90s.** UCLA at Universal City Hilton and Towers, Universal City. Fri-Sun. 17.5 hrs. $175. Contact: UCLA Extension.

September 28-October 1—**47th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research.** American Heart Association at Hyatt Regency, San Francisco. Tues-Fri. 21 hrs. Contact: AHA, 7272 Greenville Ave, Dallas, TX 75231. (214) 706-1511.

DERMATOLOGY

July 20-24—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation and UCSD at UCSD Campus, San Diego. Tues-Sat. 36 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-31—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $435. Contact: James Graham, MD, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 9-11—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronada. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

June 21-25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

August 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 15-17—**Advances in Emergency Medicine.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $450. Contact: UCSD.

October 18-22—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

November 8-12—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

May 21-22—**Chronic Renal Failure and Its Impact on Family and General Medicine.** Queen of the Valley Hospital at Clarion Hotel, Napa. Fri-Sat. $60. Contact: Becky Stephen, (707) 253-8980.

June 7-8—**Psychiatry Update for the Primary Care Physician.** University of Utah at Hyatt Regency Lake Tahoe. Mon-Tues. 9 hrs. $75. Contact: Marilyn Capener, 501 Chipeta Way, Salt Lake City, Utah 84108. (801) 584-2018.

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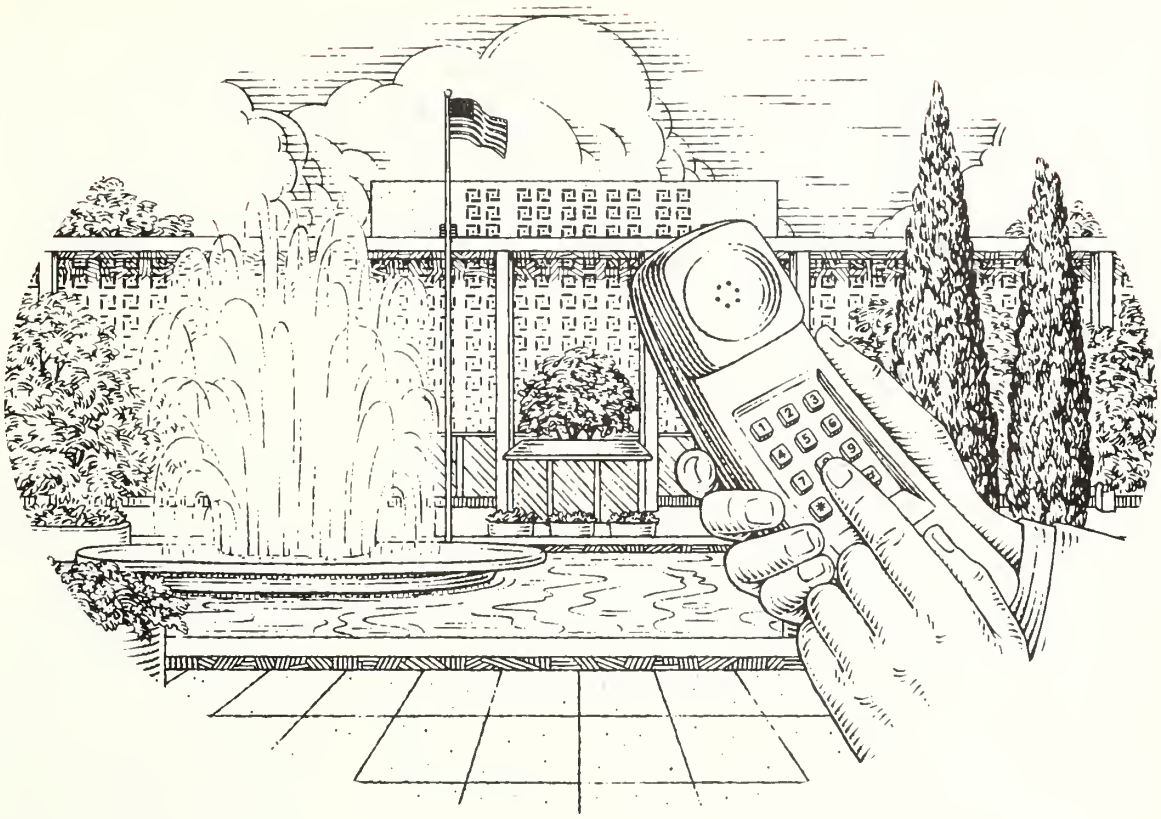

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(Continued from Page 470)

June 10-13—**Office Gynecology: A Primer for the Primary Care Physician.** UCLA at Disneyland Hotel, Anaheim. Thurs-Sun. 12 hrs. $370. Contact: UCLA Extension.

June 13-18—**17th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. $495. Contact: UCD.

June 24-27—**Primary Care Sports Medicine Conference.** UCLA at Hyatt Newporter, Newport Beach. Thurs-Sat. 20 hrs. $375. Contact: UCLA Extension.

July 5-8—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

July 22-24—**Primary Care for the 21st Century.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 17 hrs. $250. Contact: UCSD.

August 6-8—**Cardiology for the Family Physician and Internist.** Continuing Medical Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 6-8—**Primary Care Medicine: Principles and Practice.** UCSF at Nikko Hotel, San Francisco. Wed-Fri. 20 hrs. $485. Contact: UCSF.

October 6-9—**15th Semiannual Wound Management Workshop for Primary Care.** UCSD at San Diego Hilton. 17 hrs. $475. Contact: UCSD.

November 10-13—**North American Primary Care Research Group—Research Frontiers in Primary Care and Prevention.** UCSD at Hyatt Islandia on Mission Bay, San Diego. Wed-Sat. 23 hrs. $400. Contact: UCSD.

GERIATRICS

November 8-10—**Geriatrics Update: 1993.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INFECTIOUS DISEASES

May 21—**7th Annual AIDS Conference: HIV at the Crossroads—The Problems and the Promises.** Alta-Bates Medical Center at Parc Oakland Hotel, Oakland. Wed. 7 hrs. $120. Contact: Carolyn Lowery or Mary Grim, (510) 204-1590.

May 24-29—**Intensive STD Clinical Course.** Centers for Disease Control and Long Beach Department of Health Services at Long Beach Prevention Training Center. Mon-Sat. Contact: Deborah Howard, MPH, 2655 Pine Ave, Long Beach 90806. (310) 427-7421, ext. 4338.

September 2-5—**HIV, AIDS, and Women.** UCSD at La Jolla Marriott. Thurs-Sun. 15 hrs. $200. Contact: UCSD.

November 5-7—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

INTERNAL MEDICINE

May 24-28—**Advances in Internal Medicine.** UCSF at Ritz-Carlton Hotel, San Francisco. Mon-Fri. 33 hrs. $630. Contact: UCSF.

June 22-25—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Fri. 33 hrs. $630. Contact: UCSF.

August 22-27—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

October 1-3—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 18 hrs. $430. Contact: UCSF.

October 14-16—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 16 hrs. $415. Contact: UCSF.

NEUROLOGY

June 12-15—**Pharmacological Approaches to the Treatment of Chronic Pain: Current Concepts and Critical Issues.** UCSF at Doubletree Fisherman's Wharf, Monterey. Sat-Mon. Contact: UCSF.

August 5-7—**5th Annual New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. 14 hrs. $350. Contact: UCSD.

OB/GYN

November 6—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OCCUPATIONAL/ENVIRONMENTAL

June 4-5—**12th Annual Occupational and Environmental Medicine Symposium—With Postgraduate Minicourse.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

July 26-30—**Sports Medicine 1993.** UCSD at San Diego Princess Resort. Mon-Fri. 21 hrs. $350. Contact: UCSD.

October 25-29—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

OPHTHALMOLOGY

May 22—**Annual Research Symposium in Ophthalmology.** UCD at Cancer Auditorium, Sacramento. Sat. Contact: UCD.

ORTHOPAEDICS

May 19-22—**The Wrist: Problems and Challenges.** American Academy of Orthopaedic Surgeons at the Four Seasons Hotel, Newport Beach. Wed-Sat. Contact: AAOS, Course Operations, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

June 3—**Problems in Spine Surgery: Complications, Controversies and Conflict.** American Academy of Orthopaedic Surgeons at Sheraton Harbor Island, San Diego. Thurs. Contact: AAOS, 6300 N River Rd, Rosemont, IL 60018-4262. (708) 823-7186.

June 16-19—**10th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Rebecca Rimmer, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

July 25-31—**An Update in Orthopaedics.** Kaiser Permanente at Hyatt Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $395-$495. Contact: Scott Waters, 1800 Harrison, 20th Fl, Oakland 94612. (510) 987-3087.

OTOLARYNGOLOGY

May-June 1993—**Temporal Bone Surgical Dissection Courses.** House Ear Institute. Sun-Fri. 53 hrs. $1,100. Contact: Antonio de la Cruz, House Ear Institute, 2100 W 3rd St, Los Angeles 90057. (213) 483-4431, ext. 7079.

June 23-25—**20th International Conference on Cochlear Implants.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. Contact: UCSF.

November 4-6—**The San Francisco Otology, Neurotology, and Skull Base Surgery Update—1993.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 22 hrs. $395. Contact: UCSF.

PATHOLOGY

May 27-29—**9th Annual Current Issues in Anatomic Pathology: 1993.** UCSF at Mark Hopkins Intercontinental Hotel Nob Hill, San Francisco. Thurs-Sat. 19.5 hrs. $450. Contact: UCSF.

June 1-5—**Non-Gynecologic Cytopathology.** American Society of Clinical Pathologists at San Francisco. Tues-Sat. Contact: 2100 W Harrison St, Chicago, IL 60612-3798. (312) 738-1336.

August 7-14—**14th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Kapalua, Maui, Hawaii. 1 wk. 27 hrs. $950. Contact: UCSF.

October 2—**33rd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Stouffer Esmeralda Resort, Indian Wells. Sat. Contact: Sylvie Tarro, (310) 641-8152.

October 15-19—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

June 6—**Pediatric Pathology.** California Tumor Tissue Registry at Westin Mission Hills Resort, Rancho Mirage. Sun. 8 hrs. Contact: CTTR, c/o Loma Linda School of Medicine, AH 335, Loma Linda 92350. (909) 824-4788.

(Continued on Page 473)

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SERIES

1993-94 FALL/WINTER SERIES HIGHLIGHTS

JUNE 1993

1. 39th Annual Family Practice Review
June 13-19, 1993 Estes Park, CO

JULY 1993

2. 29th Annual Internal Medicine Program
July 18-23, 1993 Estes Park, CO
3. 20th Annual Renal Disease Program
July 26-30, 1993 Given Institute, Aspen, CO
4. 2nd Annual Medical Ethics Conference
July 30 - August 1, 1993 Given Institute, Aspen, CO

AUGUST 1993

5. 17th Annual Dynamic Psychotherapy Program
August 2-6, 1993 Given Institute, Aspen, CO
6. 36th Annual Pediatric Program
August 8-12, 1993 Given Institute, Aspen, CO
7. Diagnosis & Treatment of Perinatal Arrhythmias
August 13-15, 1993 Aspen, CO
8. 3rd Annual Musculoskeletal Infection Society Meeting
August 20-21, 1993 Snowmass Village, CO
9. 18th Annual Primary Musculoskeletal Care Program
August 23-28, 1993 Breckenridge, CO

NOVEMBER 1993

10. 39th Annual Family Practice Review
November 8-12, 1993 Denver, CO

DECEMBER 1993

11. Practical Issues in Infectious Diseases: Bugs & Drugs in the '90s
December 10-11, 1993 Denver, CO

JANUARY 1994

12. Reconstructive Surgery of the Hip and Knee
January 22-29, 1994 Steamboat Springs, CO
13. Contemporary Management of Unstable Coronary Syndromes
January 27-29, 1994 Breckenridge, CO

FEBRUARY 1994

14. The Colorado Conference on the Family Practice
January 30 - February 4, 1994 Denver/Breckenridge, CO

MARCH 1994

15. Horizons in Surgery
February 26 - March 5, 1994 Breckenridge, CO
16. Colorado Review of Anesthesia
February 26 - March 4, 1994 Vail, CO

CONTINUING MEDICAL EDUCATION

(Continued from Page 472)

June 11-13—**Current Concepts in Pediatric Allergy and Otolaryngology.** Children's Hospital San Diego at Catamaran Resort Hotel, San Diego. Fri-Sun. 14 hrs. Contact: Children's Hospital, (619) 576-4072.

July 8-12—**Lactation Educator Training Programs.** UCLA at Ramada Inn, Beverly Hills. Thurs-Mon. Contact: UCLA Extension.

August 23-25—**Pediatrics Update: 1993.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

May 14-19—**The Power of Art: Introduction to Medical Hypnosis.** UCSD at Colonial Inn, Del Mar. Fri-Mon. 26 hrs. $595. Contact: UCSD.

May 22—**Biofeedback, Hypnosis, and Neuro-Physiologic Response in Health and Disease.** San Francisco Academy of Hypnosis Educational and Research Foundation at Letterman Medical Center, San Francisco. Sat. $60-$100. Contact: SFAH, 615 27th St, San Francisco. (415) 282-3754.

August 3-7—**Impulse Control Disorders and Addictions: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, The Big Island, Hawaii. Tues-Sat. 24 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

RADIOLOGY

May 24-28—**Practical Body Imaging: CT, US, MRI in the 1990s.** UCSF at Marriott Hotel, Monterey. Mon-Fri. 21 hrs. $595. Contact: UCSF.

June 3-5—**2nd Annual Course in Interventional Hepatobiliary Radiology.** UCSF at Ritz-Carlton, San Francisco. Thurs-Sat. 17.5 hrs. $600. Contact: UCSF.

June 6-9—**Advanced Echocardiography and Doppler Ultrasound 1993.** American College of Cardiology at Hyatt Islandia, San Diego. Sun-Wed. 22.5 hrs. Contact: ACC, 9111 Old Georgetown Rd, Bethesda, MD 20814-1699. (800) 257-4739.

June 14-18—**MRI: A State-of-the-Art Clinical Review.** Stanford University Medical Center at Ritz-Carlton Resort Hotel, San Francisco. Mon-Fri. 27 hrs. $650. Contact: STAN.

October 18-20—**Radiology and the Non-Radiologists.** UCSD at Hyatt Regency, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

RISK MANAGEMENT

June 14-16—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at Honolulu, Hawaii. Mon-Wed. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

July 19-20—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at San Diego. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

September 27-28—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, (800) 451-7475.

SURGERY

May 20-21—**8th Annual Neurosurgery Postgraduate Course: Intracranial Tumors—Modern Management.** UCSF at Grand Hyatt on Union Square. Tues-Thurs. Contact: UCSF.

VASCULAR DISEASE

June 25-26—**Advances in Vascular Disease.** Medical Educational Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

(Continued on Page 540)

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Biomedical Science

Treatment of B-cell Lymphoma Using Peptides
A Novel Concept

KIT S. LAM, MD, PhD, *Tucson, Arizona*

Based on a paper presented at the annual meeting of the Western Association of Physicians, Carmel, California, February 5-6, 1992.

Combination chemotherapy remains the major current treatment of non-Hodgkin's lymphoma. B-cell lymphoma often has tumor-specific surface immunoglobulins called idiotypes. Clinical trials using murine monoclonal anti-idiotype antibodies as a targeting approach have shown some success. I describe a novel concept of using idiotype-specific peptides as an alternative targeting approach for the treatment of B-cell lymphoma. In brief, octapeptides that bind to the surface idiotype of the B-cell lymphoma are isolated from a large synthetic peptide library (10^6 to 10^7 peptides). Once the sequence of a tumor-specific octapeptide ligand is defined, large quantities can be synthesized and conjugated with a radionuclide (such as iodine 131). This should permit highly specific destruction of lymphoma cells that bind the labeled peptide. The theoretic advantages of this approach over the previous use of anti-idiotype antibodies are addressed.

(Lam KS: Treatment of B-cell lymphoma using peptides—A novel concept. West J Med 1993 May; 158:475-479)

Lymphoma, cancer of the lymphatic system, is classified as Hodgkin's disease and non-Hodgkin's lymphoma. Non-Hodgkin's lymphoma accounts for about 3% to 5% of the deaths from all human malignant neoplasms. About 35,000 new cases of the disease occur each year in the United States. The US incidence is 10.2 per 100,000 for men and 7.5 per 100,000 for women. Based on morphology, the National Cancer Institute's Working Formulation divides non-Hodgkin's lymphoma into three grades—low, intermediate, and high—with further subclassifications.[1] The low-grade form, which accounts for about 40% of all cases, is classified as "indolent" lymphoma. In general, chemotherapy has little effect on the overall survival of low-grade non-Hodgkin's lymphoma (median survival of 5 to 7 years), and the disease is rarely cured. In contrast, the intermediate- and high-grade forms behave more aggressively, but with combination chemotherapy at least 30% to 40% of patients can be cured.*

The current treatment options for non-Hodgkin's lymphoma are summarized in Table 1. Low-grade lymphoma, particularly in stages III and IV, is commonly treated only after symptoms are produced. Intermediate- or high-grade lymphoma is usually treated with conventional chemotherapy to attempt a cure. Radiation therapy may palliate or occasionally cure early stage disease.

*See also the editorial by M. F. Renschler, MD, and R. Levy, MD, "Overcoming the Limitations of Chemotherapy in the Treatment of B-cell Non-Hodgkin's Lymphomas—An Approach Using Radiolabeled Peptide Ligands," on pages 530-532 of this issue.

TABLE 1.—*Current Treatment Options for Lymphoma*

No treatment
Conventional chemotherapy
Radiation therapy
Biologic therapy, such as interferon alfa
Bone marrow transplantation, autologous
Monoclonal antibody, such as anti-idiotype

Biologic therapy such as interferon alfa may be useful in low-grade lymphomas,[2] and autologous bone marrow transplantation may benefit younger patients with refractory disease.[3,4] Experimental therapy with idiotype-specific monoclonal antibody has also been tried.[5-9]

Conventional chemotherapy is always nonspecific; all chemotherapeutic drugs have substantial adverse effects on normal cells. Conventional chemotherapy preferentially kills proliferating cells, which include those of the normal gastrointestinal tract, hair follicles, and the hematopoietic system. Consequently, chemotherapy often leads to notable side effects such as hair loss, gastrointestinal toxicity, nausea, vomiting, neutropenia, thrombocytopenia, and anemia. The toxicity of certain chemotherapeutic drugs may affect specific organs, such as toxicity of doxorubicin on the heart and that of bleomycin on the lungs. In contrast, antibiotics are far more specific in their action against bacteria and do not usually affect normal cells. This results in a high therapeutic index and a high curative rate for most bacterial infec-

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tions. Conventional chemotherapy has a narrow therapeutic index, and high doses can be administered only if the cells of the bone marrow can be replaced by transplantation.[3,4]

About 85% of cases of non-Hodgkin's lymphoma originate in B cells. B-cell lymphomas are unique in that many have monoclonal surface immunoglobulins, called idiotypes (Figure 1). The idiotype, specific to that tumor clone, is the only true "tumor-specific antigen." Levy

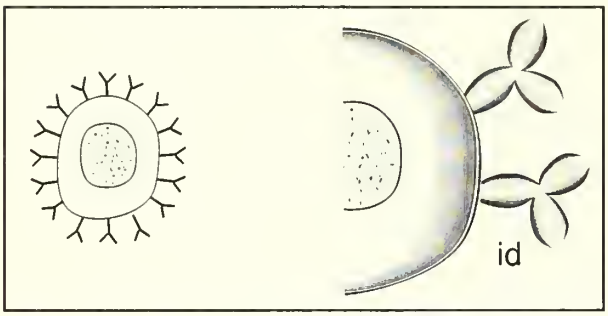

Figure 1.—The diagrams show the cell surface antibody idiotype **(id)** of B-cell lymphoma.

and co-workers pioneered in the treatment of B-cell lymphomas with murine monoclonal anti-idiotypic antibodies that are directed against these surface idiotypes.[4-8] Patients with non-Hodgkin's lymphoma have been treated with anti-idiotype antibodies alone, in combination with interferon alfa, or in combination with chlorambucil.[9] The use of anti-idiotype antibody alone (16 treatment courses) was associated with two complete responses and six partial responses. Although most of the relapsing tumors expressed surface immunoglobulin, in only five of the ten analyzed did the tumor cells react with the original anti-idiotype antibody.[9,10] Two patients with B-cell lymphoma have been treated with anti-idiotype monoclonal antibody labeled with yttrium 90.[11] This approach can potentially circumvent the emergence of idiotype-negative tumor cells because these cells may also be killed as bystanders within the tumor mass. Besides anti-idiotype therapy, therapy with pan-B–reactive murine antibody has also been tried in both the unconjugated[12] and iodinated (iodine 131) forms.[13]

To increase the therapeutic potency of monoclonal antibodies, cytotoxic agents such as chemotherapeutic drugs, toxins, or radionuclides have been coupled to the monoclonal antibodies.[14] For immunotoxins, ricin A chain, diphtheria toxin, and *Pseudomonas* exotoxin A have been most commonly used. Radionuclides such as yttrium 90, bismuth 212, iodine 125, and iodine 131 have all been used to conjugate to antibodies for immunotherapy.

Concept of Antigen-Directed Immunotherapy

Instead of using anti-idiotype monoclonal antibodies for the treatment of B-cell lymphomas, it is conceivable that a specific antigen-immunotoxin conjugate or radioactive antigen could be used that would target the surface idiotype of the lymphoma cells (Figure 2). This would permit highly specific destruction of the lymphoma cells capable of binding these labeled antigens. This concept of "antigen-directed immunotherapy" is not new; an [^{125}I]dinitrophenylated L-Tyr-L-Glu-L-Lys copolymer antigen of high specific activity has been used to deplete an antidinitrophenyl B-cell clone.[15] An ^{125}I-labeled liver-specific antigen has been used to inhibit the development of experimental autoimmune hepatitis in rabbits,[16] and an ^{125}I-labeled acetylcholine receptor has been used to reduce the severity of experimental autoimmune myasthenia gravis (EAMG) in rats.[17] Antigen-ricin A chain conjugates have been used to selectively inhibit anti-nucleoside-specific antibody production,[18] antithyroglobulin autoantibody response,[19] anti-tetanus toxoid antibody production,[20] and antiacetylcholine receptor response in EAMG.[21,22] The efficacy of antigen-directed immunotherapy has therefore been well established in various experimental systems. The treatment of chronic EAMG with antigen-toxin conjugates or radiolabeled conjugates has proved more difficult.[23] The antigen used was a macromolecule (in this case acetylcholine receptor), and its use resulted in the formation of large aggregates and nonspecific toxicity of the conjugates in tissues in which the aggregates collect. Nonspecific toxicity was also seen with antibody-immunotoxin conjugates as described earlier.

Synthesizing and Identifying a Mimotope

The major obstacle to the concept of antigen-directed immunotherapy in B-cell lymphoma is finding the antigen to which the idiotype specifically binds. That is, a "mimotope" must be found that binds to the antigen-

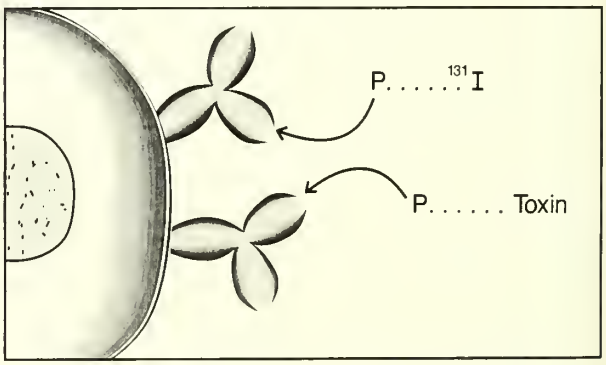

Figure 2.—Once identified, the idiotype-specific peptide **(P)** can be conjugated to either iodine 131 or a toxin for targeted therapy.

combining site of the surface idiotype. (Mimotope is defined as an amino acid sequence that will mimic the antigenic site and that will bind specifically to the antigen-combining site of the antibody molecule.) Ideally this would be accomplished by rapidly selecting the required mimotope from a large library of peptides. Such a task is enormous even for short peptides. Figure 3 shows the possible number of permutations for peptides of various lengths when all 20 L-amino acids are used in the synthesis of such a library. Even for a pentapeptide, there are 3.2×10^6 possible permutations. Synthesizing

such a library one peptide at a time is practically impossible, but substantial technical advances have been made in this area in the past five years. A system has been devised to synthesize peptides on polyethylene pins for mapping epitopes and determining mimotopes.[24] As another approach, randomly generated DNA fragments have been inserted into gene III of a filamentous bacteriophage for generating peptide libraries.[25-27] From such large phage-peptide libraries, ligands specific to two antimyohemoerythrin monoclonal antibodies,[25] an anti-β-endorphin monoclonal antibody,[26] and streptavidin[27] have been identified. Peptide ligands specific to concanavalin A have been identified using the same technique.[28,29] A technique of light-directed, spatially addressable parallel chemical synthesis of an array of 1,024 peptides simultaneously on a glass microscope slide has been developed.[30] A solution of an equimolar mixture of peptides has been generated, and the investigators proposed the concept of using such a library for drug discovery.[31] A combinatorial peptide library approach to identify peptide ligands that interact with a monoclonal antibody has been described.[32]

X	20^1	=	20
XX	20^2	=	400
XXX	20^3	=	8,000
XXXX	20^4	=	160,000
XXXXX	20^5	=	3,200,000
XXXXXX	20^6	=	64,000,000
XXXXXXX	20^7	=	1,280,000,000

Figure 3.—The number of possible permutations are shown for a random peptide if all 20 L-amino acids are used.

These previously described techniques have biologic, chemical, and practical limitations that have led to an exploration of more powerful alternative approaches to synthesize and screen peptide libraries. A simple method—"selectide technology"—has been devised that greatly facilitates the chemical production and rapid evaluation of random libraries of millions of peptides.[33] This should allow the rapid identification and sequencing of peptide ligands that bind to acceptor molecules such as the lymphoma surface idiotype. Such an acceptor molecule, defined as a macromolecule that interacts specifically with ligands, could be an antibody, an enzyme, or a biologic receptor molecule.

Briefly, in selectide technology, a "split-synthesis" method is used to synthesize on solid-phase beads a large library of peptides (1 to 10 million). In the resultant peptide library, each individual bead represents only one peptide entity (the one-bead, one-peptide concept). The peptide library is incubated with an enzyme-labeled monoclonal antibody (such as alkaline phosphatase conjugate). After thorough washing, a chromogenic substrate—for example, 5-bromo-4-chloro-3-indolyl phosphate and nitroblue tetrazolium—is added. The peptide bead that reacts with the monoclonal antibody turns dark blue. The blue bead is then physically isolated and the amino acid sequence of the mimotope determined with a protein microsequencer.[33]

In one set of experiments, a large, synthetic, random pentapeptide library was generated: XXXXX-β-ala-aminocaproic acid-ethylenediamine-resin, where X represents the 19 eukaryotic amino acids, excluding cysteine, with a total of approximately 2.5 million permutations. The monoclonal antibody used to screen the library was anti-β-endorphin. From a library of about 2 million beads, six peptide ligands were identified, all of which have close resemblance to the native ligand. Importantly, the affinity constants of three of these six selected ligands are as good as that of the natural ligand.

I plan to apply this new method to identify a peptide that has high affinity for the surface idiotype of a B-cell lymphoma and then to use that peptide for targeting treatment.

Possible Advantages of Antigen-Directed Immunotherapy

For an individualized treatment program such as the one proposed here, it is important that it can be created without undue delay. Once our methods are established, the timing should be reasonably rapid, especially with the selectide technique. Once the sequence of the mimotope is identified, large quantities of an octapeptide can be rapidly synthesized. The total time required is anticipated to be less than a month. This is considerably shorter and more economic than creating mouse monoclonal anti-idiotype antibodies (which takes 12 to 14 months).[9]

In addition to speed, the concept of antigen-directed immunotherapy using small peptides offers several distinct therapeutic advantages over the use of anti-idiotype monoclonal antibodies (Table 2):

- The peptide-conjugate will be considerably smaller than the antibody conjugate, which should allow better tissue penetration;
- Large quantities of the peptide-conjugate (such as [^{131}I]peptide) can easily be synthesized with high specific activity;
- The reticuloendothelial system uptake of the peptide-conjugate will likely be less than that of the antibody-conjugate;
- Because of its small size, the peptide-conjugate, especially the radioactive peptide, may not be immunogenic, and hence a host antibody reaction may not occur;
- D-Amino acids can be used in the peptide-conjugate synthesis and will not be readily hydrolyzed in the body;
- Using techniques in modern synthetic peptide chemistry,[34] we can modify peptide sequences with unnatural amino acid analogues and possibly increase their affinity for the idiotype, thereby increasing the therapeutic index and improving its pharmacokinetic properties.

Figure 4 summarizes a proposed scheme for the generation of lymphoma-binding peptides for antigen-

TABLE 2.—*Peptide Mimotope Compared With Murine Anti-idiotype Monoclonal Antibody os Therapy Targeted Against B-cell Lymphoma*

Therapy	*Molecular Weight*	*Tissue Penetration*	*Therapeutic Quantity*	*Chemical Modification**	*Reticulo-endothelial System Uptake*	*Immunogenic*	*Higher-Affinity Analogues*	*Time From Biopsy to Treatment*
Peptide mimotope	600-1,000	Superior	Quick and inexpensive	Easy	Negligible	Probably not	Easier	2-3 wk†
Anti-idiotype monoclonal antibody	160,000	May be a problem	Slow and expensive	Difficult	High	Possibly a problem‡	Difficult	1 yr

*An example would be radiolabeling.
†This is still theoretic.
‡Human antimouse antibody

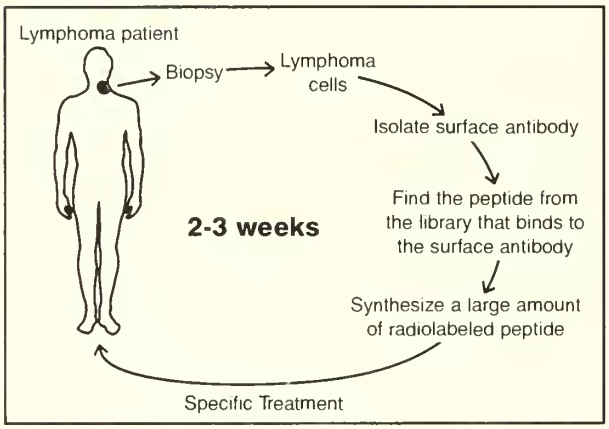

Figure 4.—A hypothetic scheme is shown for developing idiotype specific for the treatment of B-cell lymphoma peptide.

directed radioimmunotherapy. Work currently underway in my laboratory will determine peptide mimotopes for both human and murine B-cell lymphoma cell lines. Clinical trials will begin only after efficacy has been proved both in vitro and in vivo in the murine model. Antigen-directed immunotherapy is not restricted to the treatment of B-cell lymphoma. Target cells other than of B-cell lymphoma could include those of T-cell lymphoma, chronic lymphocytic leukemia, or acute lymphocytic leukemia provided that these neoplastic cells have surface idiotypes. In addition, a number of other possible applications of this technology include eliminating the B-cell clones that cause various autoimmune diseases.

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *How can you conveniently deliver the radioactive peptide to a patient?*

DR LAM: For L-amino acid-containing peptides, gastrointestinal uptake will not be practical because the peptides would be degraded. Furthermore, there are no transport systems for these peptides across the epithelial cells. An intravenous administration would be used initially for peptides previously radiolabeled and purified in the laboratory.

PHYSICIAN IN THE AUDIENCE: *Have you been able to identify a peptide that has high affinity for lymphoma idiotypes? If so, does it have the same affinity as you have shown for the anti-β-endorphin monoclonal antibody?*

DR LAM: We are currently perfecting the technique of isolating peptides, and we are just beginning to work on human and mouse lymphoma cell lines. I hope that in a few months we can answer that question.

PHYSICIAN IN THE AUDIENCE: *In his comparable work, Ronald Levy, MD, has faced two problems that you will face as well. First, will even the smaller molecules find their way through tumor tissue that is necrotic and poorly perfused? The second question concerns the specificity of killing cells with an agent tagged with something like ^{131}I or any agent that releases a penetrating γ-ray. The experience has been that no matter how specific the monoclonal antibody, the whole body is affected by radiotherapy because of the penetration of the γ-rays. So you will need an agent with a narrow emitter for killing cells, which may have to be a β-particle. Finally, B cells have an unfortunate tendency to mutate. As a result, something that may have been specific at one time will lose its effectiveness based on its inability to bind with the mutated receptor molecule. One may therefore need a cocktail or a constantly changing mixture of specific materials. The method remains innovative, however, and we thank you for that.*

DR LAM: We chose ^{131}I for initial studies because it is relatively easy to synthesize an [^{131}I]peptide in the laboratory. We can use another radionuclide that has a shorter range of radiation, however, so that it will not affect other cells. I think that the key reason that radiolabeled monoclonal antibodies affect the whole body is that the reticuloendothelial cells of the liver, spleen, and bone marrow reticulum take up the derivatized antibody. We hope that small peptides will bind only to the lymphoma target and that any unbound peptide will be rapidly excreted by the kidney. This has certainly been true for the use of ^{131}I to ablate the thyroid. As you have correctly pointed out, B-cell tumors have regressed, only to recur with an altered idiotype, usually in either the light chain or the heavy chain, but not both. We hope that the use of a radioactive peptide will also kill any mutated bystander cells with altered idiotype. In addition, because the peptide actually fits into the antigen-combining site (paratope) of the antibody molecule, it is conceivable that despite the mutation of one chain, the hypervariable region of the other chain may retain sufficient functional contact groups for the peptide mimotope to interact. In other words, the mimotopes may still be able to bind to the new paratope, although perhaps with a somewhat lower affinity. Furthermore, there are shared idiotypes.[35] Therefore, instead of using individualized treatment programs for

patients, a select panel of perhaps 20 or 30 peptides might prove sufficient to treat a relatively wide range of lymphoma cells. A combination of various peptide approaches is another possibility. All of the potential problems that you raise are definitely valid and need to be addressed.

It is also unclear what would happen when an unlabeled peptide binds to the lymphoma cell. Will the peptide enter the cell and subsequently present in a class I antigen, perhaps to be seen by a T cell, with killing of the presenting cell? Will the cell automatically undergo apoptosis? All of these questions still have to be worked out if we are to develop a truly specific targeting approach for treating B-cell lymphoma.

PHYSICIAN IN THE AUDIENCE: *Are your B-cell lymphomas monoclonal, oligoclonal, or polyclonal?*

DR LAM: For B-cell lymphoma unrelated to the acquired immunodeficiency syndrome, they are monoclonal, at least in the early stage. As noted earlier, following treatment with murine anti-idiotype antibodies, tumors will regress, but they may recur with a changed idiotype—that is, a new clone.

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Articles

Human T-Lymphotropic Virus Type I Seroprevalence Among Japanese Americans

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The epidemiology of human T-lymphotropic virus type I (HTLV-I) infection is not well defined in Japanese Americans. This impairs using approaches that could reduce viral transmission and monitor carriers for the disease. Using enzyme-linked immunosorbent assay and p21e recombinant Western blot testing, HTLV-I antibody was measured in unlinked samples from Japanese-American patients at 4 physicians' offices in San Francisco, California. Of 442 patients, 4 (0.9%; 95% confidence interval 0.25%, 2.3%) were confirmed seropositive, all with an HTLV-I rather than an HTLV-II pattern on Western blot. Seroprevalence was highest among the issei or immigrant generation (3/230 or 1.3%) compared with the second-generation nisei (1/191 or 0.5%) or third-generation sansei (0 of 17). Prevalence did not differ by age or sex, although the number of positive subjects in each subgroup was small. Of 88 patients with familial origins in endemic areas of southern Japan, none were seropositive. In this sample of Japanese Americans, HTLV-I seroprevalence was lower than in residents of endemic southern Japan but higher than among American blood donors. The prevalence was most similar to that in nonendemic areas of Japan. The public health implications of HTLV-I infection among Japanese Americans are discussed.

(Murphy EL, Varney KF, Miyasaki NT, et al: Human T-lymphotropic virus type I seroprevalence among Japanese Americans. West J Med 1993 May; 158:480-483)

Human T-lymphotropic virus type I (HTLV-I) is a human oncovirus discovered in the early 1980s[1] that causes adult T-cell leukemia[2,3] and HTLV-I–associated myelopathy/tropical spastic paraparesis[4,5] in a minority of those infected with the virus. It is transmitted by sexual intercourse,[6] by blood transfusion,[7,8] and from seropositive women to their offspring with 20% to 30% efficiency, primarily through breast-feeding.[9]

Infection with HTLV-I is prevalent in southern Japan and the Pacific islands, several Caribbean countries, and central Africa.[10] In Hawaii, HTLV-I seroprevalence of 20% has been reported in middle-aged Japanese-American men of Okinawan descent.[11] The prevalence of the virus, however, among the large population of Japanese Americans living in the western continental United States has not been studied.

Because persons infected with HTLV-I may be screened medically for HTLV-I–associated diseases and because changes in breast-feeding and sexual behavior can interrupt transmission of the virus, we studied HTLV-I prevalence among Japanese-American patients at four medical practices in San Francisco.

Patients and Methods

Population and Procedures

The study population consisted of all Japanese-American patients presenting for office visits and laboratory tests between February 7 and December 27, 1990, to four San Francisco physicians. These physicians were selected because their practices had high proportions of Japanese-American patients. Each physician reviewed the ethnicity of all patients seen during the study period.

For all patients with Japanese-American ancestry who required blood specimens for clinical laboratory tests, the physician filled out a brief data sheet. Information was obtained on age, sex, generation of residence in the United States, and whether either maternal or paternal family origins were in HTLV-I–endemic areas of Kyushu, Shikoku, or Okinawa. (This last item was added after the beginning of the survey, and data were not collected on about 25% of respondents.) Each data sheet was marked with a subject identification number, which also appeared on a set of labels that were attached to the laboratory requisition forms and the blood specimen tubes. Thus, although the data sheet and blood specimens

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SmithKline Beecham Clinical Laboratories and Physicians' Medical Center Laboratories processed the blood specimens used in this report, and Steve S. Alexander, PhD, of Cambridge Biotech Corporation provided the Western blot reagents. This work was supported in part by grants from the Dean of the School of Medicine and the Academic Senate, University of California, San Francisco. Dr Murphy is a Charles E. Culpeper Foundation Medical Scholar.

ABBREVIATIONS USED IN TEXT

ELISA = enzyme-linked immunosorbent assay
HTLV-I = human T-lymphotropic virus type I

were marked with the subject identification number, no link to a patient's identity was maintained, and informed consent was not obtained. The patient's medical record was marked after enrollment to preclude duplicate entry into the study. The study protocol was approved by the Committee on Human Research of the University of California, San Francisco.

Measurement of HTLV-I Antibodies

Clinical laboratories performing laboratory tests for the four physicians separated serum and plasma from blood specimens marked with the study labels and saved

TABLE 1.—*Demographic Characteristics of the Study Population**

Characteristic	*Men, No. (n = 179)*	*Women, No. (n = 258)*	*All Patients, No. (N = 442)*
Age, yr			
20-29	3	5	8
30-39	11	5	17
40-49	19	18	37
50-59	33	47	80
60-69	43	70	115
≥70	68	112	182
Generation of US Residence			
Issei (immigrant)	74	153	230
Nisei (2nd generation)	95	94	191
Sansei (3rd generation)	10	7	17
Unknown	0	4	4
Area of Origin in Japan			
Kyushu	17	20	37
Shikoku	12	16	28
Okinawa	0	1	1
Endemic, unspecified†	8	14	22
Other part of Japan	85	125	215
Unknown	10	3	13
Missing data	47	79	126

*Data for sex were missing from the data sheets of 5 patients and for age of 3 patients.

†Responded positively to question on origin in any of Kyushu, Shikoku, or Okinawa but did not specify which area.

the refrigerated specimens. On a weekly basis, specimens and data sheets were collected and brought to the study laboratory. Antibodies to HTLV-I were measured by enzyme-linked immunosorbent assay (ELISA, Dupont, Wilmington, Del), and specimens with absorbance values greater than 70% of the manufacturer's recommended cutoff were retested in duplicate. If the levels were still above 70% of the cutoff, the specimens were tested by the p21*env*-enhanced Western blot method (Cambridge Biotech, Rockville, Md). Specimens with reactivity to both *gag* (p19 or p24) and *env* (p21e or gp46) HTLV-I proteins were considered positive.

Statistical Analysis

The 95% confidence intervals on prevalence were calculated using the exact binomial method. Subgroup-specific seroprevalence using information from the data sheet was analyzed with the SAS-PC (SAS, Cary, North Carolina) software on a personal computer.

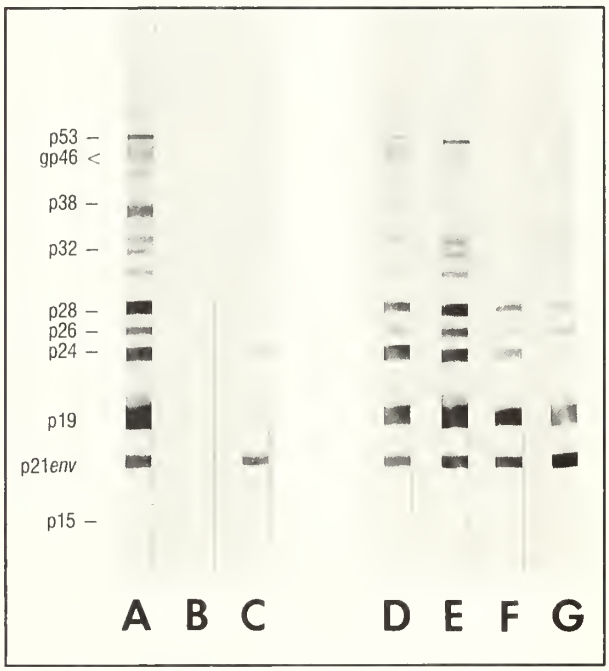

Figure 1.—We performed p21*env*-enhanced Western blot testing on blood specimens taken from Japanese Americans seropositive for human T-lymphotropic virus type I (HTLV-I). Lane A shows the HTLV-I-positive control serum exhibiting reactivity with multiple viral proteins as labeled by molecular weight. Lane B is a negative control, and Lane C is an HTLV-II-positive control serum. Lanes D through G are specimens from positive patients, all of which show p19 reactivity equal to or greater than p24 reactivity, consistent with HTLV-I antibody.[12]

Results

Study Population

Data sheets and blood specimens were available for 536 patients. On initial review of the data, 94 patients were determined to be Japanese citizens residing temporarily in San Francisco. None of these patients were HTLV-I-seropositive, and they were excluded from subsequent analysis. Table 1 shows the demographic characteristics of the 442 Japanese Americans in the study population. Women comprised 59% of the sample, and the age distribution was skewed toward older patients. Consistent with the older age of the patients, most were either issei (immigrants) or nisei (children of immigrants), with only 17 sansei (grandchildren of immigrants) in the sample. Data on familial origin in Japan were not obtained for 126 patients because this question was added to the questionnaire after enrollment had begun; origin was unknown for 13. Of the remaining 303 patients, 88 (29%) had family origins in the southern Japanese areas of Kyushu, Shikoku, or Okinawa where HTLV-I is endemic.

Seroprevalence

Of the 442 patients, 4 had repeatedly reactive ELISA results, and all 4 (0.9%, 95% confidence interval 0.25%, 2.3%) were confirmed seropositive by p21*env*-enhanced Western blot testing. All 4 seropositive specimens were at least as reactive to the HTLV-I p19 *gag* protein as to the p24 *gag* protein (Figure 1).[12] This pattern has been determined to be a reliable indicator of antibody to HTLV-I as opposed to HTLV-II.[12] Because of the unlinked nature of the study, cellular specimens for differentiating virus type by polymerase chain reaction could not be obtained from the seropositive patients.

Because of the small number of positive patients, only limited observations on subgroup-specific seroprevalence could be made (Table 2). No clear age dependence of seroprevalence was seen, although few patients were younger than 40, and prevalence was similar for men and women. An apparent trend was decreasing HTLV-I seroprevalence with each generation of residence in the United States: 3 of 230 (1.3%) issei (immigrants), 1 of 191 (0.5%) nisei (born in the United States of immigrant parents), and 0 of 17 sansei (grandchildren of immigrants). The difference between issei and nisei seroprevalence, however, did not reach statistical significance ($P = .38$, Fisher's exact test). None of the 88 patients with familial origins in the endemic areas of Kyushu, Shikoku, or Okinawa were seropositive; two who were seropositive originated from nonendemic areas, one had unknown origins, and the information on this variable was unavailable for the fourth seropositive person.

Discussion

Because of the relatively small sample size of the study, the confidence intervals on our 0.9% HTLV-I seroprevalence estimate for Japanese Americans (0.25%, 2.3%) are large; nevertheless, comparison may be made with other published values. In the endemic area of Kyushu, southern Japan, 8% of blood donors were HTLV-I–seropositive compared with 0.8% of blood donors in other areas of Japan.[13] In contrast, only 0.025% of US blood donors were HTLV-seropositive, although rates were higher in certain localities.[14] Caution must be exercised in comparing data from published studies because of different laboratory techniques and dissimilar ages of the patients in view of the strong age dependence of HTLV-I seroprevalence. For this study we used a sensitive and specific testing method[15] but had a clinic-based sampling frame and a preponderance of older patients, both of which may have inflated true prevalence rates.

Most studies have reported lower HTLV-I seroprevalence in immigrants than in the endemic populations from which they emigrated. Tajima and colleagues studied migrants aged 16 through 39 years from endemic Kyushu who were workers at a company in nonendemic Aichi prefecture and found an overall prevalence of 4%,[16] a rate not much lower than that to be expected among similarly aged residents of Kyushu. Blattner and coworkers studied Okinawan immigrants to Hawaii and found an overall seroprevalence of 20% among middle-aged to elderly men participating in a cardiovascular disease survey.[11] Rates of antibody positivity were correlated with length of childhood residence in endemic areas, and these rates increased with age even among nisei, leading the authors to hypothesize latent infection with subsequent antibody production. Ho and associates suggested that intermarriage and a higher socioeconomic status might account for the lower prevalence among immigrants.[17] Tsugane and colleagues studied Japanese immigrants to Bolivia and found HTLV-I seroprevalence of 17% in first-generation and 6% in second- or third-generation Japanese immigrants.[18] Prevalence was significantly higher among immigrants from Kyushu or Okinawa than among those from nonendemic areas of Japan.

The reasons for a lower HTLV-I seroprevalence among immigrants from endemic areas are complex. Maintenance of a stable prevalence of HTLV-I infection in a population probably requires transmission by the mother-to-child and sexual routes plus more uncommon vectors, such as contaminated blood transfusions or needles.[19] Whereas mother-to-child infection may continue in immigrants, the sexual and blood-transfusion modes of transmission become less important than in the endemic area because the sexual partner or blood donor is far less likely to be HTLV-I–infected in the adopted country, assuming cultural integration between the immigrant minority and the host country. Because mother-to-child transmission is only about 20% efficient and because only infected women will transmit the virus to the next

TABLE 2.—*Human T-Lymphatrapic Virus Seraprevalence in San Francisca Japanese Americans by Age, Sex, Generatian af United States Residence, and Area af Origin in Japan**

	No. Positive	(%)	No. Tested	P Value
Age, yr				
10-49	1	(1.6)	62	
50-69	1	(0.5)	195	
≥70	2	(1.1)	182	.95†
Sex				
Male	2	(1.1)	179	
Female	2	(0.8)	258	.81‡
Generation of US Residence				
Issei	3	(1.3)	230	
Nisei	1	(0.5)	191	.38‡
Sansei	0	(0.0)	17	
Unknown	0	(0.0)	4	
Area of Origin in Japan				
Kyushu, Shikoku, or Okinawa	0	(0.0)	88	
Other part of Japan	2	(0.9)	215	.50‡
Unknown	1	(7.7)	13	

*Data for age (3 patients), sex (5 patients), and area of origin (126 patients) were missing from data sheets.
†Mantel-Haenszel χ^2 test.
‡Fisher's exact test was done between first 2 categories.

generation through that route, prevalence should diminish notably over the first few generations in the new country.

The existence of a cohort effect on HTLV-I age-specific seroprevalence rates has also been postulated.[20] Ueda and co-workers demonstrated falling age-specific seroprevalence for cohorts of 20- to 30-year-old women between 1966 and 1988.[21] According to this hypothesis, lower HTLV-I prevalence in more recent cohorts may be at least in part the result of life-style changes that affect transmission efficiency, such as increased bottle-feeding of infants or an increased use of condoms for contraception. Finally, the existence of environmental cofactors that increase the risk of HTLV-I infection or seroconversion has been suggested.[11,22] These poorly defined factors, such as lower socioeconomic class, other infectious disease, or vector-borne infection, might be more common in an endemic area than in the host country and thus would lead to a lower prevalence of HTLV-I antibody among immigrants. Little experimental evidence exists for latent infection or vector transmission, and, although socioeconomic status has been associated with seropositivity, sociologic rather than environmental factors are more likely responsible for the association.

In conclusion, we observed a prevalence of antibodies to HTLV-I among Japanese-American patients that was lower than that in endemic areas of Japan; however, a larger study is needed to obtain more precise age- and sex-specific prevalence estimates. The decline in prevalence with the number of generations of residence in the United States is consistent with data from other studies and is probably due to a lower transmission of the virus by sexual and parenteral routes. A larger study of HTLV-I prevalence among pregnant Japanese-American women would be useful in determining the cost-effectiveness of a program aimed at screening such women for HTLV-I antibody and discouraging breast-feeding by those who are seropositive. The efficacy of such an intervention in reducing transmission from 30% to 3% has been clearly demonstrated in Japan.[23]

Pending a better estimation of age- and sex-specific HTLV-I prevalence in the general Japanese-American population, it is premature to recommend antibody testing of all such persons. Nevertheless, persons known to be infected with HTLV-I may be monitored for adult T-cell leukemia and HTLV-I–associated myelopathy/tropical spastic paraparesis with annual physical examinations and peripheral blood smears.

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Articles

Do-Not-Resuscitate Order
What Happens After Hospital Discharge?

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We observed 55 inpatients with "do-not-resuscitate" (DNR) orders to determine what happened to their DNR status after hospital discharge. All were admitted to the medical service of a Department of Veterans Affairs hospital. Of the 55 patients, 16 died in the hospital, 10 were discharged to inpatient hospice units, and 1 was transferred to an acute care hospital. An additional 19 patients were discharged to nursing homes. The other 9 patients (16% of the total) survived their hospital stays; 6 successful contacts were made with patients' spouses. In 1 case the spouse thought a DNR order was no longer desirable. In the other 5 cases the spouse said the DNR status was "probably" or "definitely" still warranted, but only 1 spouse had a written DNR order at home. We contacted 9 of the 14 house officers who had cared for the patients in hospital. Only 2 had ever written a DNR order after hospital discharge. Two house officers said they routinely discussed with family members a patient's expected dying process at home.

Unwanted resuscitation is as undesirable at home as in the hospital. Physicians should discuss future resuscitation procedures with patients who have DNR orders at the time of hospital discharge. Physicians, paramedic service directors, and policymakers also should develop protocols and standardized home DNR orders so that paramedics can honor the wishes of patients in the prehospital setting.

(Olsen EB, Lowenstein SR, Koziol-McLain J, Summers JG: Do-not-resuscitate order—What happens after hospital discharge? West J Med 1993 May; 158:484-487)

The do-not-resuscitate (DNR) order is an established means by which a patient in the hospital with a terminal condition and guarded prognosis may choose to forgo cardiopulmonary resuscitation (CPR). The DNR order is ideally written by a physician on behalf of the patient after frank and open discussion. The DNR order protects a patient's autonomy and right to refuse aggressive, painful, or frightening treatment, even if it is lifesaving.[1-5]

In most states, when a patient is discharged from the hospital there is no way to implement or legally enforce a DNR order. Prehospital care professionals (paramedics) operate under strict protocols established by local governing bodies for emergency medical services; in most jurisdictions, paramedics have a legal obligation to resuscitate all patients. Paramedics usually do not have access to reliable information about a patient's condition, prognosis, or treatment wishes. Furthermore, accurate patient identification and the validity of the DNR document itself present formidable problems.[6] In most states a call to emergency personnel (911) mandates a decisive and aggressive response by paramedics.[7] In the prehospital setting, a patient's autonomy is pushed aside because of legal mandates, practical constraints, and "treatment imperatives."

A simple solution is to tell patients' care givers to refrain from calling 911. Indeed, family members are often admonished to let patients die naturally at home. Care givers and family members are often unprepared for these distressing situations, however, or may still want to provide comfort to dying relatives.[7,8] Even in DNR situations, patients' families must be able to summon emergency personnel to treat pain or respiratory distress, provide other nonresuscitative support, and provide transportation to a hospital.

At present, no universally accepted protocols exist for prehospital DNR orders. In addition, the scant literature in this field does not document patients' or families' perceptions of a need for home DNR orders. Therefore, we studied a cohort of inpatients with DNR orders at a Veterans Affairs Medical Center (Denver, Colorado). We wanted to answer the following questions: Is there a need for home DNR orders following hospital discharge? If so, would such orders be accepted by patients and their

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ABBREVIATIONS USED IN TEXT

CPR = cardiopulmonary resuscitation
DNR = do-not-resuscitate

families? How often do physicians discuss home resuscitation with their patients? How frequently are home DNR arrangements made?

Patients and Methods

This study protocol was approved by the University of Colorado Health Sciences Center Human Subjects Committee. During a three-month period in 1988, we examined prospectively the records of all admissions to the Internal Medicine Department at the Denver Veterans Affairs hospital. We identified patients who had DNR orders by reviewing the medical records (attending, house officer, and nurses' notes), physicians' orders, and nurses' "Cardex." Patients were entered into our study if a DNR order was written at the time of admission or subsequently during their hospital stay. Patients admitted to the intensive care units were enrolled only if they survived to be transferred to the medical ward.

Each patient's age, sex, admitting complaint, and primary diagnosis, as well as the reasons for the DNR order, were recorded after an extensive review of the medical record. Each patient's clinical course was followed until death or discharge from hospital. Patients who died in the hospital and patients who were discharged to hospice care units (where DNR orders are continued automatically) were excluded from further study. Survivors were observed for at least two months after hospital discharge.

A follow-up telephone survey was then done. We attempted to contact each patient's home or nursing home. During these interviews, the patients (or their spouses or care givers) were asked the following questions: Were you aware that you (or your spouse) had a do-not-resuscitate order while in the hospital? In the event of a sudden collapse or stoppage of your heart and breathing, would you now want to be resuscitated? Would a DNR order, if it were available to you in your home, still be desirable?

In the final phase of this study, we interviewed the medical house officers who cared for these patients in the hospital. House officers were interviewed, rather than attending physicians, because house officers have primary responsibility for discharging patients. The physicians were asked if they remembered the study patient and DNR status. Next they were asked if they thought that a system for maintaining the DNR order at home would have been appropriate and if it had been considered for that patient or for any patient the house officer had cared for. The house officers were asked if they ever discussed the dying process or resuscitation options with patients or family members at the time of hospital discharge. Finally, house officers were asked if they had ever written a home DNR order or if they knew of a means by which such an order could be implemented.

Results

Patient Characteristics

During this three-month period, 55 patients admitted to the medical service had documented DNR orders. Most (54) were men, and the mean age was 68 ± 12.8 years (range 35 to 95). Their primary admission diagnoses were cancer (n = 23); emphysema or other respiratory disease (n = 11); neurologic disorder, including cerebrovascular disease, Parkinson's disease, or dementia (n = 4); sepsis or other infection (n = 4); cardiovascular disease (n = 3), the acquired immunodeficiency syndrome (n = 3); alcohol-related disease (n = 3); renal disease (n = 2); and miscellaneous conditions (n = 2).

In all patients the DNR order was clearly documented, but the basis for the DNR order was not always obvious. The DNR decision appeared to be based on the patients' wishes (n = 17, 31%), the family's decision (n = 13, 24%), or both (n = 16, 29%); in 9 cases (16%), the basis for the decision was not noted.

Hospital Disposition and DNR Status

A total of 16 patients (29%) died in the hospital and were excluded from further analysis. Ten patients (18%) were discharged to inpatient hospital care units, where DNR orders were uniformly applied. These hospice patients, in addition to a patient transferred to an out-of-state acute care hospital, were also excluded from further study.

In all, 19 patients (34%) were discharged from the hospital to nursing homes; the DNR status of these patients was known in 13 cases. In 12 of 13 cases, a clear DNR order appeared in the patient's chart at the nursing home.

Nine patients (16%) survived the hospital stay and were discharged home after an average stay of 14 days. Successful telephone contacts were made in six cases. No differences were noted between those contacted and those not contacted in sex, age, or length of hospital stay. All interviews were with the patients' spouses because the patients themselves had died (3 patients), been transferred to a nursing home out of state (1 patient), or could not be reached (2 patients). Of the three patients who had died, one died in a hospital and two at home. None of these three had resuscitation attempted. In every case, the spouses talked freely and at length with the interviewer about their husbands' illnesses.

In two of the six cases, the patient's wife was unaware or did not remember that the patient had had a DNR order written during the hospital stay. The six spouses were asked about the family's wishes for DNR orders in the period immediately following hospital discharge: Among the six cases, only one patient was thought to be so improved or stable that a DNR order was no longer appropriate. In the remaining five cases, a continuing home DNR order was judged "definitely" (2 cases) or "probably" (3 cases) desirable. The issue of DNR orders at home was absent from hospital discharge notes in all cases. One patient had a home DNR order provided by a home health nurse.

House Officer Attitudes

Of the 14 physicians who cared for the 55 patients, 9 (64%) were interviewed. Six (67%) of the house officers had considered making home DNR arrangements for their patients following hospital discharge, but only one had ever done so. Seven of the nine house officers (78%) thought that home DNR orders should be offered to patients who had such orders during their hospital stay. When asked what mechanisms could be used to secure home DNR orders for their patients, the house officers' suggestions included documenting continued DNR status in discharge orders, using visiting nursing services, and discussing with family members the patient's expected dying process and their options for action (for example, calling their private physician instead of 911).

Discussion

In this survey all patients discharged to hospice care units and 12 of 13 patients discharged to nursing homes had clear DNR orders in their medical records. This indicates acceptance of the DNR status for patients with terminal conditions. It also signifies approval for continuing the DNR status beyond the acute care setting. In contrast, only one of six patients who were discharged home had a DNR order, even though in five of these cases the patient's spouse thought it was definitely or probably still indicated. In our survey of medical house officers, only one had ever written a home DNR order. The important omissions are the failures of the responsible physicians to consider resuscitation status at the time of discharge, to discuss with family members the expected process of dying at home, and, if indicated, to write legally acceptable DNR orders for the home. These steps are as appropriate and necessary for patients residing at home as they are for patients in the hospital.

This study has several limitations. First, our sample may be unrepresentative. We studied only patients admitted to the internal medicine service of a Veterans Affairs hospital. The overwhelming majority of these patients were elderly men. The Veterans Affairs has extensive outreach services, and most patients were placed successfully in nursing homes or hospices. In addition, the physicians we polled were residents in internal medicine (ranging from intern to third postgraduate year). No attending faculty were interviewed.

In this study spouses, not the patients themselves, were interviewed. Regarding the suitability of DNR orders, patients and family members often disagree.[9]

Finally, of the original 55 patients, only 9 were ultimately discharged home, and the families of only 6 could be contacted. Our conclusions are therefore based on a small number of observations and must be considered tentative.

In this study we observed that house officers seldom discussed home DNR status with their patients. An explanation for their failure to raise this issue may be a sense that home DNR orders would not be obeyed by paramedics. Indeed, in Denver, according to current policies, a home DNR order would not be respected if the emergency system were activated by a 911 call. Without an established home DNR policy, a physician can only discuss what the patient and family are likely to experience during the terminal event and inform the family of possible courses of action.

A formal home DNR system has been successfully implemented in Anchorage, Alaska.[10] In Anchorage all procedural and legal matters regarding deaths are handled by the coroner's office. The physician of a terminally ill patient must contact the coroner to provide information and give approval for the home DNR order. The pertinent patient information is forwarded to the fire department dispatch center, which, in turn, informs the paramedics. For this protocol to work, substantial family or care-giver education must take place. A family member must call a nonemergency telephone number and use the phrase "no-code patient." When the no-code system is activated, police and emergency medical system units are dispatched "without lights and sirens." At the scene, paramedics assess vital signs and apply a cardiac monitor to confirm death.

In Hennepin County, Minnesota, an alternative prehospital protocol was established that continues to rely on the 911 emergency telephone number.[11] This system is based on the terminally ill patient's right to request limited emergency care. Two standardized, easily recognizable forms are used; one allows a patient to have a DNR order at home, and the other executes a DNR order for patients in nursing homes. The protocol requires that paramedics, on arrival, be presented an up-to-date, validated DNR document.[8] Do-not-resuscitate or do-not-intubate orders are written and defined on the document so that their meaning is obvious to patients and care givers.[11,12] To execute this system, the DNR document must be kept in a consistent and visible place, often near the medicine cabinet, where paramedics can find it easily. This form is reviewed every 12 months and validated by a home health agency that is regulated by the county health department.[8] When 911 is called, the patient will not be resuscitated or intubated; however, the patient remains eligible for hospital transport and nonresuscitative emergency treatment.[12]

As many as 1,000 cardiac arrests occur every day in the United States.[13(p3)] In many cases, out-of-hospital resuscitation attempts may countermand the wishes or best interests of the patients. Dull and colleagues performed a retrospective review of 633 adults who had cardiac arrest in 1988 in King County, Washington.[14] In 29% of these cases, the patient's cardiac arrest was an "expected, end-of-life" event; in 7% documentation indicated that the patient did not want to be resuscitated. In the same study, 95% of unwanted out-of-hospital resuscitation attempts proved futile.

As the population ages and medical interventions proliferate, more terminally ill patients will be encountered in the community. In recognition of this trend, the American College of Emergency Physicians has written guidelines for providing home DNR orders.[15] The guidelines call for a statement from the primary physician regarding

the patient's terminal illness, documentation of discussions with the patient or a guardian about the illness, and an expression from the patient or guardian that no resuscitative efforts are desired. Equally important, the order may be rescinded if the patient or family members express a wish to resuscitate, if the patient's primary physician orders resuscitative efforts to begin, or if medical personnel have any questions or doubts about the authenticity of the DNR order. The guidelines appropriately note that all prehospital DNR policies must begin with an endorsement by the local or state medical society. Furthermore, they outline steps by which local and state governmental agencies may propose comprehensive DNR legislation for prehospital settings.

Establishing a reliable and flexible prehospital DNR system is challenging. Small cities and community hospitals have operating procedures and regulations that differ from those of major urban areas. In many metropolitan areas ambulance companies, dispatch officers, physicians, and hospitals share the control of emergency medical services. In large cities, checking computer data bases for names of DNR patients would delay ambulance dispatch. In addition, the risk exists that a list may not be accurate and up-to-date. A home DNR order may be misplaced, outdated, or fraudulent, and, in some instances, positive patient identification may not be possible on site.

Many articles have discussed the importance of prehospital DNR protocols; two have reported on the successful implementation of home DNR orders.[3-7,9,16,17] Recent studies have examined the attitudes of elderly outpatients toward CPR.[18-20] This study is the first to document that a home DNR protocol is both desired by and acceptable to the families of patients with DNR orders. We also note that physicians rarely discuss death or resuscitation with terminally ill patients or their families at the time of hospital discharge. In addition, our study suggests that some patients who have DNR orders in the hospital, but who survive to return home, wish to retain the DNR orders at home. The incidental finding that some patients' spouses did not know that their husbands had DNR orders in the hospital reinforces the need for better communication among physicians, patients, and their families.

Based on the results of this study, we make two recommendations: First, physicians should routinely discuss dying and resuscitation options with terminally ill patients and their families at the time of hospital discharge. Unwanted resuscitation is as undesirable at home as in the hospital. Second, physicians, hospital administrators, medical society representatives, directors of emergency medical services, and legislators should consider the need to establish systems for home DNR orders in their communities.

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Articles

Effect of Preoperative Suggestion on Postoperative Gastrointestinal Motility

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Autonomic behavior is subject to direct suggestion. We found that patients undergoing major operations benefit more from instruction than from information and reassurance. We compared the return of intestinal function after intra-abdominal operations in 2 groups of patients: the suggestion group received specific instructions for the early return of gastrointestinal motility, and the control group received an equal-length interview offering reassurance and nonspecific instructions. The suggestion group had a significantly shorter average time to the return of intestinal motility, 2.6 versus 4.1 days. Time to discharge was 6.5 versus 8.1 days. Covariates including duration of operation, amount of intraoperative bowel manipulation, and amount of postoperative narcotics were also examined using the statistical model analysis of covariance. An average savings of $1,200 per patient resulted from this simple 5-minute intervention. In summary, the use of specific physiologically active suggestions given preoperatively in a believable manner can reduce the morbidity associated with an intra-abdominal operation by reducing the duration of ileus.

(Disbrow EA, Bennett HL, Owings JT: Effect of preoperative suggestion on postoperative gastrointestinal motility. West J Med 1993 May; 158:488-492)

Numerous studies attest to the value of psychological preparation for patients undergoing major and minor surgical procedures.[1,2] A variety of presurgical psychological interventions have been employed, with varying degrees of success. In this study we contrasted the use of specific instructions for the return of physiologic functioning with the more common practice of offering preoperative reassurance and information about what to expect after the operation.

Postoperative ileus is a natural consequence of intraperitoneal surgical manipulation and results in a cessation of intestinal movement and digestion.* A lack of motility necessitates abstaining from the oral intake of both liquids and solids until gastrointestinal activity returns. This may take as long as four or five days after an abdominal operation.[3]

Autonomically innervated organ systems such as the gastrointestinal system are amenable to instrumental learning.[4,5] Learned responses have been clearly demonstrated in the gastrointestinal system in a series of experiments by Miller and Banuazizi using curarized rats rewarded with electrical stimulation of the median forebrain bundle.[6] These investigators used rats paralyzed with tubocurarine who were artificially ventilated to control for possible skeletal muscle influence. They found that these rats could change the motility of their colon in the desired direction, either increased or decreased from baseline, when rewarded with pleasurable electrical brain stimulation.

There is also evidence of visceral learning in humans.[7-11] Several studies were reviewed by Miller[12] regarding gastrointestinal functioning, such as that of White and Taylor,[13] who reduced the frequency of ruminative vomiting in two mentally retarded children using electric shock as a punishment at the first sign of muscle activity involved in emesis. Schuster and colleagues taught patients to increase pressure in the lower esophageal sphincter by displaying the pressure to them and rewarding them for increases.[14] Schuster used instrumental learning to teach 40 patients to control fecal incontinence.[10] Patients watched by polygraph the increase and decrease of pressure in the internal sphincters. Of the 40 patients, 28 achieved either a complete disappearance of incontinence or a decrease in frequency of at least 90%.

In general, surgical preparation studies that aim only to provide information or to "reduce stress" or anxiety have minor or equivocal results.[15-18] The assumption of the model appears to be that giving information clarifies the unknown and thus reduces anxiety. The reduction in levels of anxiety then indirectly aids recovery. We call this the information-and-reassurance model. In contrast, viewing patients as potentially active participants in their surgical recovery, we provided a simple set of instruc-

*See also the editorial, "Ileus and Ignorance," by C. L. Witte and M. H. Witte, on pages 532-534 of this issue.

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tions designed to influence specific physiologic responses involved in the recovery from an abdominal procedure.

Support for this model is found in Olness and co-workers.[19] They found that children who received relaxation training and specific instructions for enhancing the production of immunoglobulins (S-IgA) had a notable increase in IgA levels from baseline. Two other groups of children, however, one that learned relaxation and received passive instructions to increase the amount of immune substances in saliva as they wished and one that received equal attention time without any instruction, did not show an increase in immunoglobulin levels. Only direct and specific instructions led to the physiologic change.

The evidence supporting the idea that bowel motility can be consciously influenced and that direct instructions can alter specific physiologic functioning indicates that an intervention given during a preoperative preparatory interview could speed the resolution of postoperative ileus.

Patients and Methods

Subjects

A clinical gastrointestinal nurse specialist selected 40 patients from a pool of presurgical patients on the gastrointestinal surgical service at the University of California, Davis, Medical Center in Sacramento, California. These patients met the following criteria:

- Scheduled for a major elective intraperitoneal surgical procedure not requiring postoperative endotracheal intubation and ventilation and expected to have a postoperative ileus.
- No previously diagnosed neurologic disease or deficit or previous psychiatric diagnosis or disease, including alcoholism and drug abuse.
- Preoperatively, no active diagnosis of any of the major determinants of gastrointestinal dysfunction that may be related to the onset or prolongation of adynamic ileus, such as sepsis, shock, cardiac disease, traumatic injury, respiratory tract infection, renal failure or uremia, hypokalemia, hyponatremia, porphyria, hypochloremia, hypomagnesemia, heavy metal poisoning, retroperitoneal hematoma, or pancreatitis.
- Age 18 to 65 years.
- English speaking.

Patients being consecutively admitted were asked to participate in the study. Five patients refused, and their rate of recovery was not monitored.

Procedure

Approval was obtained for a study using human subjects. After an introduction, patients were told that the study was designed to help speed their recovery. Following informed consent, a ten-minute interview was conducted in which information was collected to personalize the instructions for each patient. Finally, the patients were randomly allocated to hear one of two 5-minute presentations that were matched for length, either control instructions and reassurance or specific physiologic instructions for resolving ileus. All were told that their recovery depended in part on how well they responded to the instructions.

Patients in the control group received instructions unrelated to gastrointestinal motility to compare the results of specific instructions with those of an intervention of equal duration. These patients were told of the importance of postoperative deep breathing using the bedside spirometer. Patients in the experimental group received specific instructions for resolving ileus (Figure 1). The

> Because you need to eat food to bring nutrients to your body, it is important that your stomach and intestines begin to move as soon as possible after your operation. Abdominal operations cause your stomach and intestines to stop moving for a short time. In your case, this will be kept to a minimum because you will be very relaxed and comfortable. Your stomach will pump and gurgle, and you will become very hungry soon after the operation. Therefore, your stomach and intestines will begin to move and churn so that you can eat [favorite food from earlier in interview] soon after the operation.

Figure 1.—The patients in the study group were given these suggestions for the return of gastrointestinal motility.

same script was read to each patient in a natural and motivating tone of voice by one experimenter (E.A.D.). During both conditions, personal information such as favorite food, friends, and family were included in the suggestions and instructions, and general questions and concerns were addressed. All interviews took place no more than three days before the operation, either in the outpatient clinic or in a patient's hospital room.

To avoid any surgical or postoperative bias, none of the surgeons were informed that a study was taking place, and they were therefore blind to the patient's group. All postoperative data were collected by nurses who were blind to the patient's group. To assess the resolution of postoperative ileus, postoperative data included the time of the first passage of flatus. Self-reported information was used to collect data on the time to first flatus based on the work of Yukioka and co-workers, who compared the time to first flatus as noted by the patient and as recorded by a carbon dioxide analyzer, and determined that self-reports were accurate.[20]

The postoperative interview was identical for both conditions and was conducted only after ileus was resolved and the patient had started taking clear liquids. The postoperative interview consisted of inquiries about the patient's surgical and anesthetic experiences, present condition, and presence or absence of postoperative nausea and vomiting. The Stanford Clinical Hypnosis Scale was also used in the postoperative interview to assess hypnotic ability as it might relate to responsiveness to suggestion.[21]

Other medical recovery data included the time of the return of bowel sounds and the time to first taking clear liquids, length of hospital stay, and how long a nasogas-

tric tube was in place, if applicable. Length of hospital stay was defined as the time from the end of the operation to the time of the physician's discharge orders. Intraoperative, recovery, and total amounts of narcotics were also recorded because these opiates may inhibit bowel function. A history of abdominal operations, the duration of the operation, and an estimate of intraoperative bowel manipulation were also noted as possible contributors to the duration of ileus.

Results

In all, 15 women and 5 men received instructions for the rapid return of gastrointestinal functioning, and 14 women and 6 men received the control instructions and reassurance. The two groups did not differ in demographic data (Table 1).

TABLE 1.—*Demographic Data for Subjects in the Suggestion and Control Groups*

Variable	Suggestion Group Mean	Suggestion Group SD	Control Group Mean	Control Group SD
Age, yr	46.6	15.0	49.9	15.6
Height, cm	166.9	6.9	165.9	8.4
Weight, kg	73.2	20.9	78.8	26.5
Length of operation, hr	4.2	2.7	3.7	2.6
Previous abdominal operations, No.	1.4	1.8	2.4	1.7
Postoperative narcotics, mg*	108.7	117.5	87.0	67.5
SHCS scores	1.7	1.5	1.3	1.2
Time to 1st passing flatus, hr	62.1	39.2	100.1	59.6

SHCS = Stanford Hypnosis Clinical Scale

*The potencies of all pain medications were converted to morphine equivalents.

The time to the first passage of flatus was used as a measure of the resolution of ileus instead of the time to the first bowel sounds because it is a more reliable indicator of the return of coordinated bowel motility.[20] One-way analysis of variance revealed a significant difference between suggestion groups ($F[1, 38] = 5.63$, $P < .05$). The mean time to first flatus for patients who received instructions was 2.6 days (SD 1.6) compared with 4.2 days (SD 2.4) for controls.

This was a prospective study conducted in a randomized manner. Several factors have been previously identified as contributors to the duration of postoperative ileus. As would be expected, randomization distributed patients with these various characteristics evenly to the suggestion and control groups. These factors were identified as covariates and statistical analysis done to clarify their significance and ensure that a statistical aberration had not occurred. Statistical significance of the suggestion condition was found both with randomization alone and after the effects of the various covariates had been corrected. Some of the covariates included the Stanford Clinical Hypnosis Scale scores, duration of operation, amount of narcotics given intraoperatively and in the recovery room, and degree of bowel manipulation. The amount of narcotics given postoperatively was also analyzed as a possible covariate. Because subjects received several different types of narcotics intraoperatively and postoperatively, it was necessary to convert them all to a similar scale for the analysis. The potencies of all the pain medications were converted to morphine equivalents because equal potencies yield equal side effects.[22]

An independent surgeon who was blind to the patient-intervention group ranked the degree of intraoperative bowel manipulation and peritoneal irritation on a scale from 1 to 6 (Table 2). A score of 1 was assigned to a case when the peritoneal cavity was not entered, as in a properitoneal hernia repair. A score of 2 was given to cases in which the abdomen was opened but little bowel manipulation occurred, as in an uncomplicated open cholecystectomy. A rank of 3 was given when a moderate amount of bowel manipulation occurred. This included cases where several repositionings were required or a limited number of adhesions were taken down, such as a total abdominal hysterectomy with bilateral salpingo-oophorectomy. The rank of 4 was assigned when extensive bowel manipulation occurred. These were cases in which the patient was eviscerated for an extended period or one of the earlier-mentioned operations where extensive lysis of adhesions was required. The rank of 5 was assigned to cases in which a short segment of small bowel was resected or a cyst gastrostomy formed. The rank of 6 was given in cases where an extensive resection was done. This included colon resections and extensive small bowel resections with Roux-en-Y gastrojejunostomies.

TABLE 2.—*Subject Distribution for Ranking of Intraoperative Bowel Manipulation*

Rank of Intraoperative Bowel Manipulation	Cases per Group, No. Suggestion	Cases per Group, No. Control
1 Abdomen unopened	0	1
2 Limited bowel manipulation	5	2
3 Moderate bowel manipulation	6	3
4 Extensive bowel manipulation	2	6
5 Limited bowel resection	2	3
6 Extensive bowel resection	5	5

In an analysis of covariance, only the rank of intraoperative bowel manipulation and amount of postoperative narcotics were correlated with the dependent variable (time to first flatus) sufficiently to act as covariates ($r[39] = .58$, $P < .01$; $r[39] = .37$, $P < .05$, respectively). After adjustment for its correlation with the amount of postoperative narcotics and rank of intraoperative bowel manipulation, patients in the suggestion group differed significantly from controls with regard to the first passage of flatus ($F[1, 36] = 7.0$, $P < .05$). Table 3 contains the observed means for the time to the first passage of flatus and the means after adjustment for the covariates.

The data on the time of first taking clear liquids and the duration of nasogastric tube placement were similarly analyzed. Analyses of covariance were done with the

TABLE 3.—*Mean Time (in hours) of All Recovery Variables Before and After Adjusting for Amount of Postoperative Narcotics and of Intraoperative Bowel Manipulation*

	Suggestian Group		Control Group	
Variable	*Adjusted, Mean hr*	*Observed, Mean hr*	*Adjusted, Mean hr*	*Observed, Mean hr*
Time to 1st postoperative bowel sounds	29.4	29.5	45.5	45.6
Time to 1st postoperative flatus	63.6	62.1	98.5	100.1
Time to 1st postoperative clear liquid meal	86.9	83.4	115.6	119.1
Duration NG tube in place	59.2	57.5	75.0	76.6
Hospital stay	167.4	157.6	185.2	195.0

NG = nasogastric

time to first taking clear liquids or duration of nasogastric tube placement as the dependent variable, instruction condition as the independent variable, and postoperative narcotic intake and rank of bowel manipulation as the covariates.

After adjustment for correlation with the covariates, the mean time to first taking clear liquids was 3.5 days (SD 1.7) for the experimental group compared with 5.0 days (SD 3.5) for controls. This trend was in the desired direction, but it was not statistically significant ($F[1, 36] = 2.82$, $P = .10$). The mean duration of nasogastric tube placement for the suggestion condition was 2.5 days (SD 2.8), and the mean for the control condition was 3.1 days (SD 3.4). Again, the difference between these two means was not statistically significant ($F[1, 36] = .80$, $P > .05$), but the trend was in the desired direction. It should be noted that a nasogastric tube had to be reinserted in two patients, one in each group, and no differences were detected between groups regarding frequency of nausea and vomiting.

The length of hospital stay was also analyzed using an analysis of covariance, with the estimate of bowel manipulation as the covariate. The experimental condition had a mean duration of stay of 6.6 days (SD 7.2) compared with 8.1 days (SD 5.3) for controls. This difference was not statistically significant ($F[1, 37] = .60$, $P > .05$).

The Stanford Clinical Hypnosis Scale scores had a nearly significant negative correlation with time to first passage of flatus ($r[39] = -.32$, $P = .05$). Subjects with a shorter duration of ileus scored somewhat higher on the scale. This finding is consistent with past research reviewed by Wadden and Anderton, who concluded that hypnotic ability is positively related to the effectiveness of treatment of involuntary physiologic variables, such as pain, warts, and asthma.[23]

To ascertain if hypnotic ability was necessary for the instructions to be effective, a multiple analysis of covariance was done to determine whether there was a significant interaction between experimental condition and Stanford Clinical Hypnosis Scale scores. The time to first passage of flatus was used as the dependent variable, and the amount of postoperative narcotics and rank of intraoperative bowel manipulation were again the covariates. Experimental condition and Stanford Clinical Hypnosis Scale scores were used as independent variables to ascertain whether there was a significant interaction between the two regarding the determination of time to first flatus. This interaction was not significant ($F[4, 25] = .95$, $P > .05$), indicating that giving suggestions can be effective regardless of patients' susceptibility to suggestion.

Discussion

Verbal instructions before major operations can influence physiologic recovery. Patients who received instructions for the early return of bowel motility had a significantly decreased time to first passage of flatus compared with controls who heard an intervention matched for length and content but without the specific instructions ($P < .05$). The duration of hospital stay was reduced an average of 1.5 days in patients who received the five-minute set of instructions (this difference was not significant, however). Based on a minimum room rate of $800 per day, this difference saved patients in the experimental group an average of $1,200.

The nonsignificant results obtained for the time to first clear liquid intake were probably due to hospital procedure and not specifically to patient recovery. Unlike the time to first flatus, the time to first clear liquid intake is dependent on both a patient's physician and the cafeteria staff. Variable delays occur from the time to first flatus until a physician's orders are written for a clear liquid diet. Furthermore, patients' intake of clear liquid is delayed because they can be served only at meal time. Meal orders are sometimes lost or filled out incorrectly (for example, the patient receives a normal meal instead of a clear liquid meal). These delays compromise the accuracy of this variable as a measure of the rate of patient recovery. The nasogastric tube data were subject to similar inaccuracies.

Although the results for several of the more indirect measures of recovery, such as length of hospital stay, were not statistically significant, the trends were always in the desired direction. The influence of suggestion on these variables did not seem as clear, probably in part because of hospital procedures. A somewhat larger and more homogeneous sample would be necessary before significant levels could be reached.

The lack of interaction between the experimental condition and hypnotic ability scores suggests that these two variables are independent. That is, the instructions and the context in which they are received are important re-

gardless of a patient's susceptibility to suggestion. Therefore, all patients can benefit to some degree from suggestions that are given in a believable context.

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Articles

Barriers to Prenatal Care for Low-Income Women

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Inadequate prenatal care is associated with poor birth outcomes. Recognizing barriers to care is necessary to improve results. Postpartum in-hospital interviews were conducted with women admitted through emergency departments with no physician of record (n=69) in 8 Sacramento hospitals during April and May 1991. A focus group of local obstetrician-gynecologists was used to determine physicians' attitudes about caring for low-income women. We undertook the study in response to an increased number of "no doc" births. The inability to find a physician willing to accept them was reported by the women as the single largest barrier to obtaining care, cited by 64% of women overall and 96% of those who tried but were unable to obtain care. Transportation difficulties were a problem regardless of women's success in obtaining care and were ranked as the top barrier by women who never tried to obtain care. Physicians cited administrative difficulties and reimbursement levels of Medi-Cal plus extra care requirements and resource dependency of low-income patients as barriers to caring for this population. The value ascribed to prenatal care by women and physicians' perceptions of women's attitudes about care contrasted sharply. The link between poor women and physicians providing obstetric services can be fragile. The difficulty finding physicians willing to take them indicates that these women need special support services to ensure adequate care during pregnancy.

(Aved BM, Irwin MM, Cummings LS, Findeisen N: Barriers to prenatal care for low-income women. West J Med 1993 May; 158:493-498)

Prenatal care is generally associated with improved birth outcomes, but between a third and a fourth of all pregnant women in the United States do not obtain early, continuous prenatal care.[1] In California in 1989, 7.2% of infants were born to women who had no prenatal care or obtained it only in the third trimester.[2] Nonwhite women and those on Medi-Cal (Medicaid) or without health insurance coverage are significantly less likely than others to secure care.[1]

A major contributor to the difficulties in gaining access to obstetric services is the declining number of physicians practicing obstetrics. About one of eight obstetricians has discontinued providing obstetric care in the past several years.[3] The access problem is further exacerbated by the decreasing physician participation in Medi-Cal. In 26 northern California counties, a 13.5% drop in the number of physicians offering obstetric services and a 20% attrition rate among those accepting new Medi-Cal patients have occurred in the past two years. In Sacramento County, the largest suburban county in this area, the number of obstetricians dropped by 16% during this period (Sierra Health Foundation, "Access to Prenatal Care in Northern California: 1990 Update," Sacramento, Calif, June 1990). No new prenatal clinics opened in this geographic area during the period, and the university hospital's department of obstetrics and gynecology reduced its caseload.

Physician shortages notwithstanding, myriad factors affect the use of prenatal care services. Serious efforts to understand and reduce barriers to the use of prenatal care services are especially important for low-income women because poverty status is inexorably linked to the risk of pregnancy-related complications and poor birth outcomes. Postpartum in-hospital interviews of women with little or no prenatal care in New York City,[4] Texas,[5] and Los Angeles[6] have shown that financial obstacles and women's beliefs and attitudes about prenatal care are the major impediments to early and continuous prenatal care services. Other issues that have been recognized as barriers to health care services in general include problems with transportation and child care, excessive waiting time for new appointments and during clinic visits, language barriers, and cultural differences between patients and physicians.

Hospitals across the United States have reported a growing number of women presenting at emergency departments for delivery who have no physician of record. This means that, although a woman may have received some prenatal care during the pregnancy, she is not currently under care at the time of delivery. "No doc" births have increased as a proportion of total deliveries at each of the four largest obstetric hospitals in Sacramento County and make up more than one of every five births at the local university hospital.

We report a two-part study examining reasons cited by postpartum women for their failure to obtain prenatal

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care and factors cited by obstetricians for their reluctance to accept pregnant Medi-Cal patients. The study was undertaken by a nonprofit human services planning organization on behalf of the county medical society, hospital association, public health department, and community clinics in Sacramento County in response to a growing shortage of obstetric providers in the county and an increasing number of obstetric admissions through hospital emergency departments. The purpose of the study was to identify barriers to prenatal care services from patients' and physicians' perspectives and to plan a countywide strategy to increase access to care.

Patients and Methods

Patient Survey

Postpartum in-hospital interviews were conducted with all women admitted through emergency departments who gave birth in eight Sacramento-area hospitals without having a physician of record during April and May 1991. (The only unique characteristic of births during this period is the higher volume of births in spring months.)

To identify women with no link to an obstetric provider at the time of delivery, investigators contacted hospital obstetric department managers daily between April 1 and May 10, 1991, to determine if any women had been admitted without having a physician of record. All women presenting under such circumstances were asked by hospital staff after the birth if they would consent to be interviewed about their use of obstetric services. Women whose babies had died were not asked to participate in the study. Interviews were conducted by an ethnically and linguistically diverse pool of community health outreach workers and by nurse practitioners and midwives from Planned Parenthood and generally lasted from 45 minutes to an hour.

An interview instrument based on questionnaires used in similar interview projects was developed and adapted to emphasize issues of particular concern in Sacramento County (Community Services Society, "Prenatal Care Study of New York," unpublished data, 1990).[7] The questionnaire used both open-ended and closed questions to identify barriers to and perceptions about the value of prenatal care. Interviewers first read 36 possible influences on the use of prenatal care in consistent order and asked women whether each had been a major issue, somewhat of an issue, or not an issue in obtaining care and which of the 36 was the single most significant barrier. In the open-ended questions that followed, women were asked without prompting to describe the problems that kept them from receiving care during pregnancy. Answers to open-ended questions, which allowed women to volunteer information such as alcohol and drug use and to speak in their own words, were not analyzed differently from close-ended questions.

Physician Focus Group

Seven obstetric-gynecologic physicians representing the diverse mix of the Sacramento-area obstetric community were invited and agreed to participate in a three-hour focus group conducted by the county medical society. The physicians were selected for their breadth of involvement in professional organizations and interactive opportunities with colleagues and were representative of sex and ethnic profiles among Sacramento obstetricians. The objective of the session was to solicit physician perceptions about the problem of inadequate prenatal care for low-income women in Sacramento and possible solutions for addressing it. Because the physicians were extremely active in the medical community and likely to have perspectives beyond their own practices, they were also asked to represent the views of most of their obstetric-gynecologic colleagues. Although "low-income patient" was intended to be defined broadly, physicians' responses indicated that the term became analogous to "Medi-Cal patient." Also evident from physicians' comments was the common perception that all women on Medi-Cal are high-risk patients.

TABLE 1.—*Distribution of Women by Selected Background Variables, According to Use of Prenatal Care*

Variables	Total		Some Care		No Care, Tried		No Care, Did Not Try	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Total	69		26	(38)	23	(33)	20	(29)
Age, yr								
≤19	10	(14)	7	(70)	2	(20)	1	(10)
20-29	42	(61)	15	(36)	14	(33)	13	(31)
≥30	17	(25)	4	(24)	7	(35)	6	(35)
Race or Ethnicity								
White, non-Hispanic	26	(33)	8	(31)	12	(46)	6	(23)
White, Hispanic	18	(26)	6*	(33)	4	(22)	8	(44)
African American	19	(28)	9	(47)	5	(26)	5	(26)
American Indian	4	(6)	2	(50)	1	(25)	1	(25)
Asian	2	(3)	2	(100)	0	(0)	0	(0)
High School Graduate†								
Yes	36	(53)	18	(50)	8	(22)	10	(28)
No	32	(47)	8	(25)	14	(44)	10	(31)
Parity								
0	8	(12)	5	(62)	3	(38)	0	(0)
1	15	(22)	9	(60)	3	(20)	3	(20)
2	15	(22)	5	(33)	5	(33)	5	(33)
3	14	(20)	4	(29)	8	(57)	2	(14)
4+	17	(25)	3	(18)	4	(24)	10	(59)

*One respondent was reported as both Hispanic and American Indian.
†Schooling data not provided for one respondent.

A series of ten open-ended questions solicited information about why physicians were dropping obstetrics, what the greatest barriers were to seeing Medi-Cal patients, how these barriers could be reduced, why the physicians thought more women did not obtain prenatal care, and who needed to be involved to improve access to prenatal care for low-income women. The OptionFinder computerized decision-making system (Option Technologies, Mendota Heights, Minnesota) was used to sort physicians' responses in order of importance.

Results

Characteristics of the Women

A total of 95 women gave birth without a physician of record in eight Sacramento-area hospitals during the six-week study period in April and May 1991, representing 3.4% of the 2,725 births in the county during this period. Of these women, 72 (76%) consented to in-hospital interviews and 69 provided usable responses. Of the total group, 16 (17%) declined to be interviewed, 4 women (4%) were not asked for interviews because their babies had died, and 3 women (3%) were discharged before an interviewer arrived. The demographic characteristics of women who did not consent or were not asked for interviews were not substantively different from those of the women who participated in the study. Differences in the use of alcohol and drugs may have contributed to the reason some women declined to participate in the study.

The distribution of the 69 women by selected background characteristics according to their use of prenatal care is shown in Table 1. About 38% of the women (26) reported that they had had at least one prenatal visit to a physician during their pregnancy. About a third of the women had received no care but had tried to obtain it. Another 19 (28%) had received no care and did not try to obtain it. Women defined "trying" to obtain care by their own interpretation.

The mean age of all women interviewed was 26 years. Ten (14%) of the women who gave birth without a physician of record were age 19 or younger. As a group, the teen women were much more successful in obtaining some care during pregnancy. Whereas years of schooling did not differ substantially among the women, graduation from high school seemed to be related to success in obtaining prenatal care; a greater proportion of high school graduates who tried to obtain some care were able to do so. The women who made no attempt to find prenatal care were divided equally between those with 12 years of schooling and those with fewer.

Notable differences were recorded among women by racial and ethnic group relative to obtaining prenatal care. Hispanic women were overrepresented among the women who received no care and did not try to obtain it. This was predominantly the case for Hispanic women who were Mexican immigrants. The greatest proportion

TABLE 2.—*Major Barriers to Prenatal Care Reported by Women, According to Use of Prenatal Care*

	All Women, (n=69)		*Some Care, (n=26)*		*No Care, Tried, (n=23)*		*No Care, Did Not Try, (n=20)*	
Major Barrier	*Rank*	*%*	*Rank*	*%*	*Rank*	*%*	*Rank*	*%*
No one taking new patients	1	64	1	59	1	96	8	35
Transportation	2	53	2	33	2	65	1	65
Fare for transportation	3	37	9	19	5	43	2	55
Distance to care	4	34	6	22	7	35	3	50
Difficulty getting appointment	5	33	4	30	4	48	17	20
Didn't know where to go	6	31	12	15	3	52	10	30
Problems with Medi-Cal	7	29	2	33	6	39	--	--
Child care problems	7	29	5	26	12	22	14	25
Family problems	9	26	6	22	--	--	5	40
Felt fine, no need to go	9	26	12	15	9	26	5	40
Pregnant before, knew all	11	23	22	7	9	26	5	40
Couldn't afford care	11	23	16	11	--	--	4	45
No telephone	11	23	9	19	9	26	14	25
Felt depressed	14	20	16	11	12	22	10	30
Denial of pregnancy	14	20	6	22	--	--	10	30
Attitude of physicians, nurses	--	--	9	19	--	--	--	--
Unaware of pregnancy	--	--	16	11	8	30	--	--
Afraid of examinations	--	--	24	4	--	--	8	35
Hassled about smoking	--	--	24	4	--	--	10	30
Afraid of child custody	--	--	16	11	--	--	--	--
Clinic hours inconvenient	--	--	16	11	--	--	--	--
Couldn't see same physician	--	--	16	11	--	--	--	--
Parents knowing	--	--	22	7	--	--	--	--
Afraid to confirm pregnancy	--	--	24	4	--	--	20	15
Hiding pregnancy from others	--	--	24	4	--	--	20	15
Hassled about drinking	--	--	24	4	--	--	20	15
Provider not responsive	--	--	24	4	--	--	--	--
Don't like doctors	--	--	--	--	--	--	17	20
Long wait during visit	--	--	12	15	--	--	--	--
Ambivalence about pregnancy	--	--	12	15	--	--	14	25
Drug use	--	--	24	4	--	--	17	20

of women who reported trying, but not succeeding, to obtain care were white, non-Hispanic; these women represented almost half of that group. African-American women seemed to be the most successful at obtaining care: Nine of the African-American women in the study (47%) reported receiving some care.

Of the women interviewed, 61 (88%) had one or more children in addition to the newborn. Whether a woman had additional children and the number of children she had appeared to have influenced her ability and effort to obtain care; the more children a woman had, the less likely she was to receive prenatal care or attempt to obtain care.

Patient-Reported Barriers to Care

The inability to find a physician was reported by women as the single largest barrier to obtaining care, as shown in Table 2. Failure to find a physician who was accepting new patients was characterized as a major barrier by 44 (64%) women overall and by 22 (96%) of the women who tried but were unable to obtain care. Among women who did not try to obtain care, problems finding a physician did not rank among the most serious barriers. Their difficulties in obtaining obstetric services resulted from not seeking care until the third trimester; arriving in the Sacramento area late in their pregnancy; being dropped by a physician, usually because of missed appointments or drug use; being regarded as high risk; and being unable to find a physician who would accept new Medi-Cal patients.

The second most significant barrier to care was lack of transportation, cited by 36 (54%) women. Transportation appeared to be a more serious problem for those women who had obtained no care, whether or not they tried to obtain it; 28 (65%) of these two groups reported this as a major barrier. Other transportation-related variables that ranked high as major barriers—and highest for the women who did not try to obtain care—were fare for transportation (ranked third and reported by 37% of women) and distance that a woman had to travel to the physician (ranked fourth and reported by 34%).

The inability to afford care and problems related to Medi-Cal were important barriers to care for women. Women with some prenatal care ranked Medi-Cal problems second along with lack of transportation. Not being able to afford care was ranked the next highest problem after transportation variables among women who did not try to obtain prenatal care. Although virtually all (99%) of the women interviewed had applied for Medi-Cal at some time in their lives, Medi-Cal presented a problem for at least a third of the women. In addition to the challenge of locating a Medi-Cal provider, other difficulties described by the women included length of time from application to eligibility, difficulty completing the application form, not knowing at first that they were eligible, inconvenient location of Medi-Cal offices, inability to obtain required information, and fears about applying. Of the 32 (46%) women not on Medi-Cal when they became pregnant, nearly all tried to qualify, and three quarters were successful in obtaining Medi-Cal coverage by the time of delivery. On average, most women were approaching the third trimester of pregnancy by the time that they initiated the application process; the mean stage of pregnancy at the time of application was 5.6 months. Only 1 of the 69 women in the study was covered by health insurance, and she was enrolled in the Kaiser-Permanente system.

Inadequate child care was cited as a barrier by 21 women (30%) but was a more serious problem for those women with some care. Difficulty making an appointment because of not having a telephone, reported by about a quarter of all women, also ranked higher for women who received some care. Not knowing where to go for care was cited by 22 women (31% of all) but ranked third and was reported by 22 women (52%) who tried unsuccessfully to obtain care. A third of the women who tried to but did not obtain care reported not knowing they were pregnant early in the pregnancy as one of the reasons for failing to get care.

The use of drugs was a serious barrier to care in this population. In the open-ended questions, some women reported being dropped from care because of drug use or being afraid to keep appointments for fear of disclosure. While the methods of the study precluded obtaining an objective assessment of drug use, aggregate toxicity data of the "no doc" women made available by one of the larger hospitals showed that 57% (54/95) of these women tested positive for alcohol and illicit substances. This figure is consistent with data from a universal screening study in which 63% of women having babies with no prenatal care tested positive for alcohol or illicit substances.[8]

Several motivational or behavioral issues were reported by the women as barriers to their seeking care. The two most prevalent overall were feeling fine and thus believing that they did not need care and having had a previous pregnancy and believing that care was unnecessary. These attitudes were expressed by 8 of the women (40%) who did not seek care. Another barrier that ranked high was depression. Although this was not an important issue for the women who had some care, 5 of the women (22%) who had made unsuccessful attempts to obtain care and 6 of those who had not tried (30%) indicated that feeling depressed was an important reason for not obtaining prenatal care. Needing energy to deal with family problems ranked eighth overall as a barrier to care but was fifth for women who did not try to obtain care and for women with some care. Women who did not try to obtain care also reported that trying to ignore their pregnancy (6, or 30%) and feeling ambivalent about it (5, or 25%) kept them from seeking care.

More than 95% of women (66) stated that getting routine prenatal checkups was "very" or "considerably important." Although women who did not try to obtain care rated the value of routine care slightly lower than women who had tried unsuccessfully to obtain care or women who had received some care, 15 of this group (75%) still considered prenatal care very important.

Physician Characteristics

Six of the seven obstetrician-gynecologists in the physician focus group were in solo or small-group private practices. The seventh physician had recently left private practice to direct the obstetric services of a large community clinic. Two of the physicians in private practice had recently dropped obstetrics from their practices; the remaining four physicians in active obstetric practice indicated that they intended to stop providing obstetric services by the time they reached age 55—about 10 years away for most of them. The total number of deliveries in the four obstetric practices ranged from 150 to 500 deliveries per year. The mean number of years since completion of an obstetric residency for the physicians was 18.9 years with a range of 7 to 29 years.

Physician-Reported Barriers

The factors described by physicians as contributing to their reluctance to provide prenatal care for Medi-Cal women are displayed in Table 3. Similar to the results of other surveys in California, physicians reported the Medi-Cal reimbursement *process* as the single most important reason for not accepting any or more Medi-Cal patients.[9,10] (The reimbursement *level* was tied for second in importance.) The frustration of not being paid in a timely manner and being continually challenged about charges and procedures was seen as the primary reason for dropping or not participating in the Medi-Cal program. For physicians who accept Medi-Cal patients, finding specialists to take their patients for consultations or referrals is difficult for the same administrative and financial reimbursement reasons that the obstetricians identified.

TABLE 3.—*Physician-Perceived Barriers to Providing Prenatal Care Services to Women on Medi-Cal*

Barrier	*Rank Order*	*Frequency**
Administrative paperwork and billing process	1	7
Patients more difficult to care for, require more resources	2	6
Level of reimbursement	2	6
Hard to find appropriate referrals	4	5
Lower compliance than private-pay patients	4	5
Not neat and clean	6	4
Difficulty relating to patients	6	4
Patient attitude of services as a right	8	3
Patient unwillingness to discuss birth control postpartum	8	3
Fear of lawsuits	8	3

*Frequency of mention among the 7 obstetrician-gynecologist participants.

Physicians in this group thought that Medi-Cal patients were generally more difficult to care for and required more resources than patients with private insurance, ranking this as second in importance as a barrier to caring for them. They said that a case-management system or financial incentives to physicians willing to spend more time with Medi-Cal patients would be positive ways for the health care system to address this barrier. The physicians also regarded Medi-Cal patients as less compliant with keeping appointments and following physicians' instructions and believed that Medi-Cal women generally do not place the same value on prenatal care as do private-pay patients. Although some of the physicians were opposed to the idea of patient incentives, others suggested that financial or other incentives (particularly related to transportation and child care assistance) would improve compliance rates.

Despite studies that suggest otherwise, the physicians believed that Medi-Cal patients were more likely than private-pay patients to file lawsuits and to be substance abusers.[11-13] They said that these perceptions continued to be barriers to providing care for the Medi-Cal population. The obstetrician-gynecologists also acknowledged that "physician problems" in relating to Medi-Cal patients because of cultural and socioeconomic differences and patients' personal hygiene habits contributed to their own and their colleagues' reluctance to serve this population. For example, they suggested that the medical society might develop a patient brochure on "standards for a healthier pregnancy" to help women understand the importance of personal cleanliness.

Finally, the physicians were asked their opinions about the use of nurse midwives to expand access to prenatal care for low-income women. Most of the physicians were concerned about the perceived high-risk status of Medi-Cal patients and said that it was inappropriate for midwives to see these patients. They also noted that hiring midwives may not be cost-effective. Midwives spend more time with patients, increasing the unit cost of service and compounding the problems of increasing salaries and decreasing reimbursement from managed-care contracts and Medi-Cal.

Discussion

The results of this study show that the primary barrier to care for poor women who give birth through emergency department admissions with no physician of record is finding a physician who will accept them, particularly in the last weeks of pregnancy, or who will not drop them because of noncompliance or life-style differences. Our findings indicate that the link between pregnant Medi-Cal women and physicians providing obstetric services can be fragile. The impression is that women who initiate care in their first trimester are not high risk, do not use drugs, reside in one county for the duration of their pregnancies, and never or rarely miss appointments will probably be able to obtain care from private-practice physicians. Women who do not meet these criteria, on the other hand, have a more difficult time obtaining care.

The difficulty experienced by low-income women in finding physicians willing to care for them indicates that this population of women needs special support services to ensure adequate care during pregnancy. Among these services are programs that help connect women with willing providers and that employ a monitoring system to

ensure that the connection is made and kept. In view of the transportation problem expressed by most of the women in this and other studies, offering transportation assistance through bus and taxi vouchers or volunteer drivers also seems necessary to ensure compliance with keeping appointments, thereby decreasing physicians' frustration with frequent "no-shows." Programs that are designed to assist private physicians to serve patients with multiple health and social problems are more likely than referral services alone to be successful in increasing the use of prenatal care services.

Although physicians in this study recognized the extra care and resources that women on Medi-Cal often require, the cumbersome payment process and the low level of Medi-Cal reimbursement make physicians less willing to see these patients in their private practices. Simplifying the eligibility procedure for patients and the reimbursement process for physicians would doubtless increase the number of low-income women able to get early and continuous prenatal care. Supplying physicians with information about resources for substance abuse treatment (provided that such resources exist in the community) might also encourage more physicians to maintain resource-dependent patients in their practices.

The value assigned to prenatal care by women contrasted sharply with physicians' perceptions of women's attitudes about care in our study. Physicians judged Medi-Cal patients as having a low regard for prenatal care, but the women in this study ascribed considerable importance to obtaining care during pregnancy. Although studies have shown that women who believe prenatal care is important are more likely to obtain care beginning in the first trimester, attitudes toward the value of prenatal care are not always predictive of behavior.[14] Despite the belief expressed by 95% of our patients that prenatal care was very or considerably important and should be started early, nearly a third did not even try to obtain care. Some women—especially those with previous uncomplicated pregnancies and healthy newborns—do not seek care because they think pregnancy is a normal event not requiring medical attention unless problems arise; however, the high value placed by most women on getting prenatal care indicates that barriers of money, inability to find or keep a physician, cultural differences, drug use, and fear may thwart a woman's intention to obtain care. Two thirds of the women in our study reported that they made efforts to overcome these problems; only half were successful, although not throughout the pregnancy because they still gave birth without having a physician of record.

Our study is limited by the absence of a group obtaining continuous prenatal care to serve as a control. The women in this study were different from other women who gave birth in Sacramento during this period in that they were poorer and depended more on Medi-Cal as their source of payment. Medi-Cal births, which are not evenly distributed among area hospitals, constituted 39.8% of all births in the county and increased by 22% as a proportion of all births over the three-year period preceding this study. The study women were also unevenly distributed among the youngest and oldest age groups, again similar to other studies of prenatal care utilization.[6,15] Although our selected sample of women may not be representative of all pregnant women who are poor and have trouble finding physicians to care for them, the sample comprised all of the women in Sacramento who delivered without physicians of record within a given period.

Conclusions drawn from physicians' perceptions are constrained by the inherent limitations in the use of focus groups. Using expert panels and focus groups, which tend to be small, is a common method for gathering information in the fields of medicine and health care when empiric data are not available. The profile of our physicians was appropriate for Sacramento County. Although physicians were not prompted in identical ways to patients, their analogous responses to the questions of barriers, fears, perceptions, and values suggest correspondences on these issues.

The results of our study affirm the importance of understanding patient and physician concerns that impede access to prenatal care, as well as shedding additional light on the reasons some physicians are reluctant to provide obstetric care to poor women. The problem will most likely persist until fundamental changes in the health care delivery and financing systems take place. The critical importance of early and continuous care requires us to consider why women cannot or do not get prenatal care and to devise appropriate means to ensure that they do.

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Conferences and Reviews

34-Year-Old Woman With Hypotension, Respiratory Failure, Fever, and an Abdominal Mass

Moderators
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Discussants
HELEN E. PILLSBURY, MD; COLLEEN J. BERGIN, MD; KENNETH L. VOSTI, MD; KENNETH L. MELMON, MD; *and* CYNTHIA CLINKINGBEARD, MD

This discussion was selected from the Department of Medicine Morbidity and Mortality Conference held at the Stanford University Medical Center, Stanford, California, on March 20, 1991. Philip C. Lee, MD, Chief Resident, Department of Medicine, edited the conference.

We present a case in which hypotension, metabolic acidosis, respiratory failure, and acute renal failure rapidly developed in a young woman after a single dose of the β-blocker penbutolol sulfate. Associated clinical findings were fever, leukocytosis with a leftward shift, rash, and a right upper quadrant mass. The initial clinical impression included septic shock—the toxic shock syndrome—with concomitant myocardial depression. Her course was notable for frequent episodes of hemodynamic instability with recurrent pulmonary edema and labile blood pressure and heart rate. Imaging of the abdomen showed a right adrenal mass, and the correct diagnosis was confirmed. Her clinical condition stabilized dramatically once appropriate pharmacologic therapy was instituted.

Case Presentation

HELEN E. PILLSBURY, MD*: The patient, a 34-year-old woman, was transferred from another hospital for the evaluation of hypotension, acidosis, respiratory failure, fever, and acute renal failure.

History of Illness

The patient was apparently well until three days before admission when pharyngitis, headache, cough, shortness of breath, nausea, vomiting, fatigue, palpitations, and diaphoresis developed. She did not have fevers or chills. On the day before admission, she was found by her private physician to be hypertensive, and a single 10-mg dose of penbutolol sulfate—a nonselective β-adrenergic antagonist—was administered orally. Over the next several hours, she had worsening dyspnea and lethargy and presented to a local hospital.

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The patient's temperature was 37°C (98.6°F), pulse rate 80 beats per minute, systolic blood pressure 90 mm of mercury, and respiratory rate 38 per minute. She was agitated, and the findings of the initial examination were notable for nondistended jugular veins, rales in both lung fields, and cool, cyanotic extremities.

The patient was given 2 liters per minute of oxygen per nasal cannula, and a specimen of arterial blood revealed a pH of 7.24, a $Paco_2$ of 35 mm of mercury, and a Pao_2 of 49 mm of mercury. With the patient receiving 100% oxygen by nonrebreather mask, a second arterial specimen showed a pH of 7.08, a $Paco_2$ of 40 mm of mercury, and a Pao_2 of 65 mm of mercury. An endotracheal tube was rapidly inserted, and the patient was placed on ventilatory support and admitted to the intensive care unit.

A blood chemistry panel gave the following values: potassium, 7.0 mmol per liter (7.0 mEq per liter); bicarbonate, 14 mmol per liter (14 mEq per liter); blood urea nitrogen, 5.0 mmol per liter (14 mg per dl); and creatinine, 106 μmol per liter (1.2 mg per dl). The leukocyte count was 21.3×10^9 per liter (21,300 per μl) with 0.26 (26%) band forms; the hematocrit was 0.41 (41%); and the platelet count was 437×10^9 per liter (437,000 per μl). The serum creatine kinase level was elevated at 259 U per liter, with 0.166 (16.6%) attributable to the MB fraction. The prothrombin time was 10.9 seconds, and an activated partial thromboplastin time was 35.9 seconds.

Soon after admission, the patient's temperature rose to 39.6°C (103.3°F), and she was anuric. A Swan-Ganz pulmonary artery catheter was placed; cardiac output was 2.1 liters per minute with systemic vascular resistance of 3,882 dynes-second per cm^5, and the pulmonary capillary wedge pressure was reported to be elevated.

(Lee PC, Gocke CD, Harris ED Jr, et al: 34-Year-old woman with hypotension, respiratory failure, fever, and an abdominal mass. West J Med 1993 May; 158:499-505)

Reprint requests to Philip C. Lee, MD, Department of Medicine, S102, Stanford University Medical Center, Stanford, CA 94305.

Treatment with dopamine hydrochloride, 3 μg per kg per minute; amrinone; nitroglycerin; and digoxin, 0.25 mg, was initiated intravenously. Furosemide, bumetanide, and mannitol were administered to promote urinary output. The patient was also started empirically on a regimen of vancomycin hydrochloride, tobramycin, and erythromycin for possible infection. Later that same day, laboratory studies showed further elevations of levels of blood urea nitrogen, 12.5 mmol per liter (35 mg per dl); creatinine, 203 μmol per liter (2.3 mg per dl); and creatine kinase, 388 U per liter, with an MB fraction of 0.31 (31%). An echocardiogram demonstrated global hypokinesis. The patient was transferred to Stanford University Medical Center, Palo Alto, California, for the evaluation of "possible myocarditis."

Medical History

The patient's medical history was notable for the spontaneous vaginal delivery of a child nine months before admission. There was a question of hypertension during her pregnancy, but details were not available. She was gravida 1, para 1, and her last menstrual period was 14 days before admission and reported to be normal. She said she did not use tampons. The patient was not taking any medications (except those noted earlier), denied alcohol, cigarette smoking, or illicit drug use, and had no known allergies. The patient's father had a history of hypertension and coronary artery disease, but the family history was otherwise unremarkable. She was employed as a software engineer and emigrated from Taiwan six years ago.

Stanford Hospital Admission

Physical Examination

On arrival, the patient's temperature was 40°C (104°F), pulse rate 140 per minute, blood pressure 105/70 mm of mercury, and respiratory rate 12 per minute by mechanical ventilation. She was a thin young woman with an endotracheal tube in place. The patient was alert, oriented, and could provide written responses to questions. Her skin was cool but not cyanotic. Her head and neck were normal. Scattered rales were present at both lung bases, but she otherwise had good breath sounds throughout. Aside from tachycardia, her heart was normal. The abdomen had normal bowel sounds, the liver size was normal, and the spleen could not be felt. A large, firm mass was noted in the right flank and right upper quadrant, associated with some mild right upper quadrant tenderness. Rectal and pelvic examinations yielded no abnormalities. Extremities showed no edema, and no neurologic abnormalities were elicited.

Laboratory Data

A blood chemistry panel revealed the following values: sodium, 142 mmol per liter; potassium, 3.8 mmol per liter; chloride, 105 mmol per liter; bicarbonate, 18 mmol per liter; blood urea nitrogen, 15.3 mmol per liter (43 mg per dl); creatinine, 257 μmol per liter (2.9 mg per dl); and glucose, 5.9 mmol per liter (107 mg per dl). The total protein level was 69 grams per liter (6.9 grams per dl); albumin, 34 grams per liter (3.4 grams per dl); calcium, 1.9 mmol per liter (7.6 mg per dl); phosphorus, 1.80 mmol per liter (5.6 mg per dl); total bilirubin, 11.9 μmol per liter (0.7 mg per dl); alkaline phosphatase, 134 U per liter; alanine aminotransferase, 973 U per liter; aspartate aminotransferase, 1,569 U per liter; lactate dehydrogenase, 10,352 U per liter; uric acid, 0.77 mmol per liter (12.9 mg per dl); and cholesterol, 4.1 mmol per liter (157 mg per dl). The leukocyte count was 38.6×10^9 per liter with 0.58 polymorphonuclear leukocytes, 0.36 band forms, 0.04 lymphocytes, and 0.01 monocytes. The hematocrit was 0.50 with a mean corpuscular volume of 89 fl, and the platelet count was 200 to 300×10^9 per liter. A serum creatine kinase level was 744 U per liter with an MB fraction of 0.04 (4%), and the erythrocyte sedimentation rate was 3 mm per hour. The prothrombin time was 19.3 seconds, and an activated partial thromboplastin time was 41.5 seconds. Analysis of a catheterized urine specimen revealed a specific gravity of 1.010, pH 7.0, reaction for protein 1+ and for blood 2+ by dipstick, 1 to 5 leukocytes per high-power field, 1 to 5 erythrocytes, and no casts. A specimen of arterial blood drawn while the patient was breathing 90% oxygen through an endotracheal tube showed a pH of 7.47, a Pa_{CO_2} of 26 mm of mercury, and a Pa_{O_2} of 87 mm of mercury. An electrocardiogram showed sinus tachycardia at a rate of 150 per minute with nonspecific ST-segment and T-wave abnormalities. The chest radiograph showed mild interstitial edema and normal cardiac size.

Hospital Course

On the first day of the hospital course, the patient's condition was stabilized. Her hemodynamic measurements were as follows: the central venous pressure was 7 mm of mercury, pulmonary arterial pressure 20/0 mm of mercury, pulmonary capillary wedge pressure 4 mm of mercury, cardiac output 2.8 liters per minute, and systemic vascular resistance, 2,000 dynes-second per cm^5. After aggressive fluid resuscitation, the pulmonary arterial pressure was 36/16 mm of mercury, the pulmonary capillary wedge pressure was 8 mm of mercury, cardiac output 11.0 liters per minute, and the systemic vascular resistance 552 dynes-second per cm^5. Adequate urine output resumed, and the dosages of dobutamine, amrinone, and nitroglycerin were tapered. No further dosages of digoxin were given.

The differential diagnosis included myocarditis, sepsis, and pheochromocytoma. A myocardial biopsy specimen showed no evidence of active inflammation. With improvement in the patient's hemodynamic condition, oxygenation also improved. She continued to be febrile, and several specimens were obtained for culture. Specimens from bronchoscopy showed many neutrophils, but appropriate stains were negative for microorganisms, including *Pneumocystis carinii*. A regimen of erythromycin, ceftazidime, and clindamycin phosphate was started empirically (doses of vancomycin and tobramycin, with prolonged half-lives due to the patient's renal insuffi-

ciency, had been given the previous day). An ultrasonographic examination of the abdomen showed no evidence of hydronephrosis, but a 5-cm right adrenal mass was identified, most consistent with adrenal hemorrhage or tumor. Intravenous hydrocortisone sodium succinate was started empirically, and a subsequent morning serum cortisol level was 1,987 nmol per liter (72 μg per dl) (normal, 138 to 662 nmol per liter). Specimens of urine and serum for the assay of catecholamines were not obtained because the patient was receiving dopamine and dobutamine, and fresh frozen plasma was administered to correct a mild disseminated intravascular coagulation.

On the second day, a generalized, painless, nonpruritic erythroderma developed that spread centripetally from the hands to the arms and eventually to the chest and face. Her hemodynamic state was unchanged, showing persistently increased cardiac output and decreased systemic vascular resistance. Her pulse rate was 110, and her blood pressure was 130/80 mm of mercury. Meanwhile, her pulmonary status and coagulation measurements continued to improve. A dermatology consultant described the rash as classic for the toxic shock syndrome. The clinical syndrome of septic hemodynamic physiology, high fevers, marked leukocytosis with a leftward shift, disseminated intravascular coagulation, abnormally elevated values on liver function tests, hypocalcemia, and acute renal failure seemed consistent with the clinical syndrome; an infectious disease consultant concurred.

On the third day of the hospital course, the patient began coughing up large amounts of bloody, frothy sputum through the endotracheal tube. At the same time, she became hypertensive to 192/112 mm of mercury and tachycardic to 140 per minute. The pulmonary capillary wedge pressure rose from 11 to 30 mm of mercury, oxygen saturation declined, and a chest radiograph was consistent with pulmonary edema. The patient's clinical condition improved with prompt diuresis and afterload reduction with the intravenous administration of sodium nitroprusside. Meanwhile, she remained febrile to 39.8°C (103.6°F). Although the rash did not desquamate and began to resolve, the leukocyte count remained at 24×10^9 per liter with 0.42 band forms, the platelet count decreased to 59×10^9 per liter, and mild disseminated intravascular coagulation continued. None of the cultures, including those done at the other hospital, grew organisms, and additional cultures of specimens swabbed from vaginal, perianal, and pharyngeal mucosal sites were obtained in considering the diagnosis of toxic shock syndrome. Other notable laboratory values included blood urea nitrogen, 13.9 mmol per liter (39 mg per dl); creatinine, 230 μmol per liter (2.6 mg per dl); alanine aminotransferase, 482 U per liter; aspartate aminotransferase, 503 U per liter; and lactate dehydrogenase, 5,763 U per liter.

On the fourth day, magnetic resonance (MR) imaging of the upper abdomen revealed hemorrhage in the right adrenal mass. An echocardiogram showed moderate to severe global left ventricular hypokinesis. Episodes of hemodynamic lability and instability continued. While she was sleeping, the patient's blood pressure fell to 70/40 mm of mercury with a pulse rate of 90 per minute. After a 250-ml intravenous bolus of a normal saline solution, the blood pressure rose to 170/110 mm of mercury with a pulse of 140. Pulmonary edema again developed but resolved spontaneously, although her blood pressure remained extremely labile throughout the rest of the night.

On the fifth day, the diagnosis of pheochromocytoma was considered more likely in the clinical setting of hemodynamic lability and the presence of a right adrenal mass on cross-sectional images. Dopamine was discontinued, and α-adrenergic blockade with phentolamine mesylate was initiated with improved blood pressure control. Although she remained febrile, all cultures remained negative for the growth of microorganisms.

Over the next few days, the patient's pulmonary status improved dramatically, and the endotracheal tube was removed. On further questioning when the patient was better able to communicate, she described a five-year history of increased sweating involving her head and upper torso, hypertension during pregnancy, orthostatic hypotension after delivery, headaches and dizziness since then, and episodes of nausea and vomiting provoked by stress and standing that were relieved within minutes by lying down. The patient was observed to have episodes of hypertension and tachycardia shortly after finishing a meal and when the right side of the abdomen was palpated.

Her blood pressure was well controlled pharmacologically with a combination of α- and β-adrenergic blockade, initially with phentolamine and the continuous intravenous administration of esmolol hydrochloride (a short-acting, cardioselective β_1-adrenergic antagonist) and later using labetalol hydrochloride alone (with both selective α_1- and nonselective β-adrenergic blocking actions). The patient became afebrile, and the leukocytosis resolved. On the eighth hospital day, labetolol therapy was discontinued after an episode of hypotension, and a regimen of phenoxybenzamine hydrochloride—an α-adrenergic receptor blocking agent—was started. Propranolol hydrochloride was later added for better control.

On the 13th day, the assay results of the 24-hour urine collection and serum for catecholamines became available (Table 1) and were consistent with the diagnosis of pheochromocytoma. A follow-up echocardiogram now showed normal left ventricular size and contractility. A surgical procedure was carried out.

Radiologic Findings

COLLEEN J. BERGIN, MD*: The first imaging modality used in this patient to demonstrate the inhomogeneous 5-cm suprarenal mass was ultrasonography. A subsequent examination with MR imaging showed the presence of hemorrhage within the mass and showed the intermediate signal intensity on T1-weighted images and very bright

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TABLE 1.—*Assay for Catecholamines From a 24-Hour Urine Collection and Serum*

Analyte	Catecholamines						
	Metanephrine	*Normetanephrine*	*Total Metanephrine*	*Epinephrine*	*Norepinephrine*	*Dopamine*	*Vanillylmandelic acid*
Urine*	21,571	31,437	53,008	3,370	4,979	996	96
Normal	34-300	110-620	140-820	0-25	0-100	80-440	0-6
Plasma†	--	--	--	66,098	>120,000	4,307	
Normal				<90	<600	<135	

*Urine catecholamines are given in μg/24 hours.
†Plasma catecholamines are given in pg/ml.

signal intensity on T2-weighted images characteristic of pheochromocytoma (Figure 1).[1]

The most appropriate initial imaging study for a patient presenting with a mass in the right upper quadrant is an ultrasound examination. Either MR or computed tomographic imaging is the next examination of choice for further evaluation of an adrenal mass. With MR imaging, intravascular contrast material is not necessary for defining retroperitoneal abnormalities; this may be particularly important in some patients with pheochromocytomas because contrast material can occasionally precipitate hypertensive crises. In addition, tissue specificity of the adrenal glands is notably better on MR than on computed tomographic images because of the long T2 measurements of pheochromocytomas relative to other adrenal lesions.[1]

Clinical Discussion

EDWARD D. HARRIS, Jr, MD*: Why was the patient initially thought to have the toxic shock syndrome?

KENNETH L. VOSTI, MD†: The toxic shock syndrome represents a constellation of clinical and laboratory findings reflecting multiple organ involvement. This syndrome most commonly develops as a complication of the use of highly absorbent tampons during menstruation in young women.[2] This patient was a young woman who was seen initially because of a short prodrome of myalgias, vomiting, and fever and who was found to have a pronounced leukocytosis with a leftward shift. She rapidly became acutely ill with hypotension and an evanescent, erythematous rash. In addition, there was evidence of gastrointestinal (nausea and vomiting), hepatic (elevated values on liver function tests), renal (acute renal failure), and hematologic (thrombocytopenia) involvement.

Although her clinical and laboratory findings were consistent with a diagnosis of toxic shock syndrome, certain features argued against this diagnosis. For instance, the patient's last menstrual period was 14 days before her symptoms began and was reported to have been normal. She did not use tampons and did not have a vaginal discharge. These factors alone do not exclude the diagnosis, since in the past few years a nearly equal proportion of cases of the toxic shock syndrome reported to the Centers for Disease Control were due to a focus of infection with *Staphylococcus aureus* at an extragenital site.[3] Although cultures of the blood have generally been negative in patients with the toxic shock syndrome due to *S aureus*, cultures of the vagina, cervix, or an extragenital focus are more likely to yield the organism. The persistent inability to recover *S aureus* from any of the multiple sites cultured failed to provide important support for this diagnosis.

Infections with other organisms may be associated with a toxic shock-like syndrome. In recent years, the association of severe infections with group A β-hemolytic streptococci with a toxic shock-like syndrome has

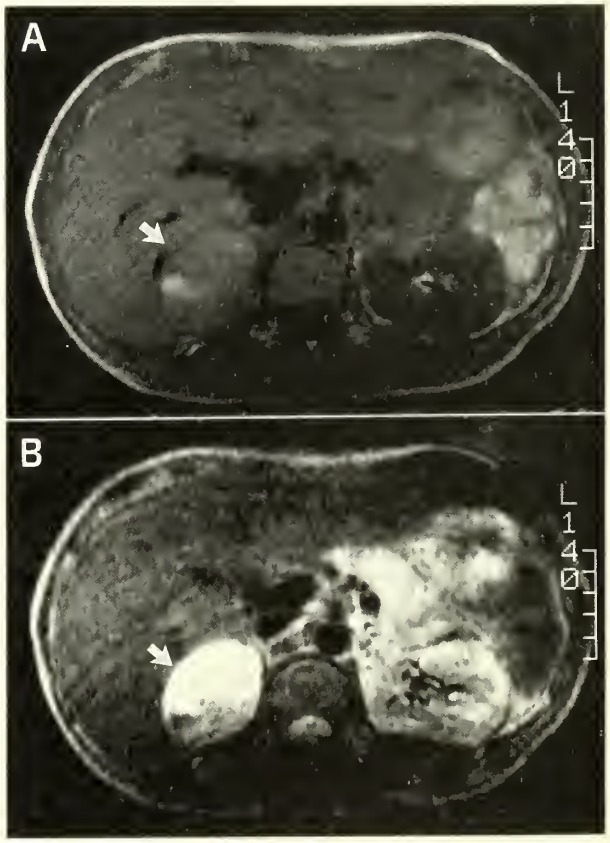

Figure 1.—Magnetic resonance images of the abdomen show a large tumor of the right adrenal gland (**arrows**). **A**, The T1-weighted image (TR/TE 300/15 ms) demonstrates the inhomogeneous suprarenal mass. Bright signal on this image is consistent with hemorrhage. **B**, The T2-weighted image (TR/TE 2,000/70 ms) shows the markedly increased signal intensity of the tumor characteristic of a pheochromocytoma.

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received considerable attention. Patients with this disorder typically present with clear evidence of infection of the skin, soft tissues, or both. There is no predilection for the disorder in young menstruating women or for involvement of the genital tract. In contrast to the usual absence of documented bacteremia among patients with the toxic shock syndrome due to *S aureus* infection, blood cultures were positive for group A β-hemolytic streptococci in about 70% of patients with a toxic shock-like syndrome.[4]

It was appropriate to continue empiric antimicrobial therapy in this patient with presumed sepsis until a more specific or alternative diagnosis could be established.

DR HARRIS: How was the diagnosis of pheochromocytoma made?

KENNETH L. MELMON, MD*: The diagnosis of pheochromocytoma is often delayed and requires a high degree of clinical suspicion.[5-7] A careful historian could have elicited this patient's constellation of symptoms earlier and may have been able to avert this life-threatening episode.

Once the patient was extubated and able to communicate during her hospital stay, she gave a history classic for pheochromocytoma.[5-7] She had noticed increased sweating over the past five years (mostly involving her head and trunk) that was severe and striking. Symptoms of dizziness, nausea, and vomiting were brought on by stress at work and by standing and were always relieved within minutes by lying down or more gradually by sitting. In fact, most of the signs and symptoms for which the patient was initially seen can be explained by an excessive catecholamine state. Even pyrexia, leukocytosis, and thrombocytopenia can occur in patients with pheochromocytomas.

Interestingly, this patient did not have a pheochromocytoma crisis during her pregnancy and parturition nine months earlier, both of which can precipitate crises.[6] Given the size of the tumor, it is certain that the pheochromocytoma was present during her pregnancy. In retrospect, she was indeed found to be hypertensive during her pregnancy, and several episodes of orthostatic hypotension developed that were particularly pronounced immediately after delivery. This case demonstrates how clinically unpredictable pheochromocytomas can be.

The most prominent tip-off for a pheochromocytoma in this patient was her history of orthostasis in the presence of hypertension, with or without the coexistence of a cardiomyopathy. Any patient with intermittent hypertension and orthostatic hypotension in the absence of severe intravascular volume contraction should be evaluated for a pheochromocytoma.[6] The pronounced hypotension seen in this patient could be explained by the large amounts of epinephrine produced by the tumor. Moreover, the rapid acceleration of her signs and symptoms during her course was consistent with hemorrhage in the tumor tissue, leading to the release of excessive amounts of catecholamines. In fact, pulmonary edema and cardiovascular collapse are unusual but known presentations for pheochromocytomas[8-10]; prompt recognition of the syndrome is imperative so that appropriate therapy can be instituted.

This patient's clinical signs led to appropriate laboratory tests that are definitive in the diagnosis of this disease.[5,6] As in this patient, the measurement of catecholamines and their metabolites from both urinary and plasma sources is diagnostic.[11,12] Various substances have been reported to interfere with these measurements, however.[6,13] This patient was initially given dopamine, which delayed the biochemical testing for pheochromocytoma. If the levels of other "nondopamine" catecholamines are markedly and disproportionately elevated, the diagnosis can still be made in the presence of intravenous dopamine therapy.

DR HARRIS: How was the patient's pheochromocytoma managed once the diagnosis was made?

CYNTHIA CLINKINGBEARD, MD*: It is worthwhile to emphasize a few key points about the events leading up to this patient's hospital admission and near-death. Although she was ventilator-dependent and could not describe the events preceding her illness, the combination of an extremely labile hemodynamic condition and a right adrenal mass could have prompted more aggressive confirmation of the diagnosis and earlier treatment with α-adrenergic blockade. In retrospect, she presented with hypertension, congestive heart failure, and other symptoms related to her pheochromocytoma.

The untoward consequences of administering a β-blocker alone to a patient with pheochromocytoma are well known,[8,13] and this case is a clear example of the hazard. The "unopposed α-adrenergic stimulation" that follows can lead to severe peripheral vasoconstriction, hypertensive crisis, severe left ventricular dysfunction, and ultimately cardiovascular collapse.[8]

This patient's condition stabilized rapidly after phentolamine therapy was started. Once α-blockade is adequate, then a β-adrenergic antagonist can be added to control tachycardia, dysrhythmias, or both. Esmolol, a short-acting intravenous β-adrenergic blocker, is an excellent choice in the intensive care unit setting. When this patient's condition appeared to stabilize, her regimen was changed to labetalol, which possesses both α_1- and β-adrenergic blocking activity. Although labetolol has not been approved for treating pheochromocytoma, it is often used in these patients and can be effective. Remember that different batches of drugs may contain significantly varying ratios of α_1- and β-blockade, which can adversely affect patient hemodynamics. Although some groups advocate the use of the α_1-adrenergic antagonist prazosin hydrochloride,[5,7] this patient was ultimately treated with phenoxybenzamine—a long-acting α-adrenergic blocker—and propranolol. Her condition remained stable on this regimen.

Although there is some debate regarding the optimal time for a surgical procedure, removal of the tumor is

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clearly the definitive therapy for this disease.[5,14] In general, surgical resection of a pheochromocytoma should be done as an elective procedure once the expected hypovolemia is corrected with α-blockade and volume replacement. Surgeons and anesthesiologists need to anticipate the severe hypertension, arrhythmias, severe hypotension, and hemorrhage that can ensue. Patients should have central venous and intraarterial monitoring

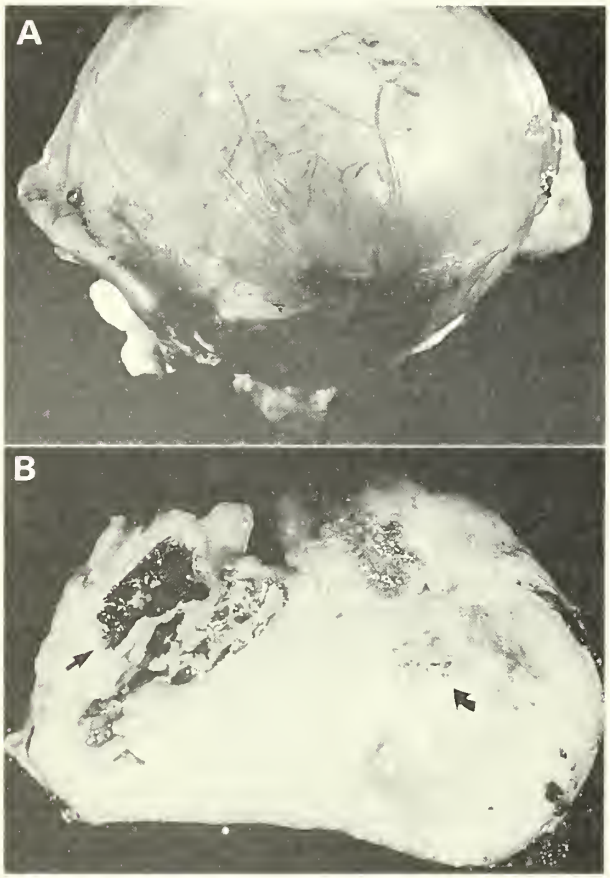

Figure 2.—The specimen shows tumor occupying the body of the right adrenal gland. A, Note the smooth, uninterrupted external surface and the uninvolved adrenal cortex at each pole. B, The cut surface shows a fleshy tumor with regions of hemorrhage (**straight arrow**) and chalky-white necrosis (**curved arrow**).

during the operation, and short-acting agents should be used in the management of intraoperative events.

In this patient, all urinary catecholamine levels were within normal limits when measured four months after the operation. The patient returned to work and was feeling well, except that she had missed her menstrual periods since the time of her hospital admission. A pregnancy test was positive, and a year later, mother and baby are both doing well.

Pathologic Findings

CHRISTOPHER D. GOCKE, MD*: The right adrenal gland was removed. The adrenal medulla was replaced by a single tumor nodule 5 cm in diameter (Figure 2). Residual adrenal cortex was present at each pole of the specimen, and the tumor was entirely confined within a rim of attenuated cortical tissue. The cut surface of the mass was yellow-gray with a prominent vascular pattern and areas of hemorrhage and necrosis.

Microscopic examination of the tumor revealed a delicate, well-vascularized stroma, separating sheets of large pale gray to pink tumor cells into a distinct "zellballen," or alveolar, pattern characteristic of pheochromocytomas (Figure 3). The tumor cells possessed round vesicular nuclei with small, centrally placed nucleoli and had abundant granular cytoplasm. Adjacent adrenal cortex was unremarkable.

More than 90% of pheochromocytomas are benign, and surgically removing the tumor is usually curative. Unfortunately, there are no gross or microscopic characteristics of malignant pheochromocytomas that serve to distinguish them reliably from their nonmalignant counterparts. Large tumor size, extensive necrosis, and small cell size have been proposed as discriminators of malignancy, but their predictive value remains unclear.[15] The diagnosis of a malignant neoplasm is ultimately based on findings of local invasion or metastatic spread.

Bilaterality occurs in about 5% of spontaneous pheochromocytomas; often the diagnosis of these are made postoperatively when urine catecholamine levels fail to decrease to normal. In contrast, bilateral pheochromocytomas are present in about 65% of familial cases—multiple endocrine neoplasia type II, or Sipple's syndrome.[16] Multiple pheochromocytomas may also be present in association with other diseases—most notably von Hippel-Lindau disease and neurofibromatosis. No history of endocrine adenomas existed in this patient's family, nor did she exhibit any other endocrine abnormalities. Her postoperative urine catecholamine levels were within normal limits.

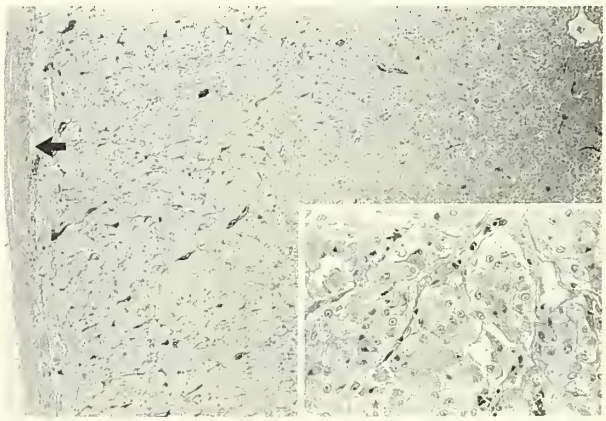

Figure 3.—Histologic section of the pheochromocytoma shows a fine vascular network subdividing the tumor cells into a clustered ("zellballen") pattern. The mass is circumscribed by a thin fibrous capsule, in some areas containing atrophic adrenal cortex (**arrow**). The tumor cells are large and polygonal with single nucleoli (**inset**). Note the absence of nuclear pleomorphism and mitotic figures (hematoxylin and eosin stain; original magnification ×40, inset ×250).

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Anatomic Diagnosis

Right adrenal pheochromocytoma.

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Antiplatelet Therapy—Part II

SCOTT H. GOODNIGHT, MD; BRUCE M. COULL, MD; JOHN H. McANULTY, MD;
and LLOYD M. TAYLOR, MD, *Portlond, Oregon*

We summarize current information about aspirin and other antiplatelet drugs in patients with cardiac and vascular disease. For each indication, we briefly summarize the rationale for the use of antiplatelet therapy and describe the findings of relevant clinical trials. We propose recommendations for the use of these agents in clinical practice. In Part 2, we discuss the use of antiplatelet agents in coronary angioplasty, atrial fibrillation, artificial cardiac valves, stroke, and peripheral vascular disease. In Part 1, we reviewed the use of antiplatelet therapy for the primary and secondary prevention of myocardial infarction, in conjunction with coronary thrombolysis, in patients with unstable and chronic stable angina, and following coronary artery-saphenous vein bypass grafting.

(Goodnight SH, Coull BM, McAnulty JH, Taylor LM: Antiplatelet therapy—Part II. West J Med 1993 May; 158:506-514)

We continue our review of the indications and optimal use of antiplatelet therapy for patients with vascular and cardiac disease. Again, readers requiring more information or discussion are directed to the first 17 reviews referenced in Part I (the April 1993 issue, pp 385-392).

Percutaneous Transluminal Coronary Angioplasty

Rationale

Percutaneous transluminal coronary angioplasty (PTCA) widens the arterial lumen but disrupts the atherosclerotic plaque, producing injury to the vascular endothelium. Coronary artery occlusion following PTCA may occur early (within 24 hours of the procedure) in about 3% of patients, or late (over the next few years) in as many as 30%.[1] Early occlusion may result from the creation of intimal flaps or arterial dissection, but may also be platelet mediated as a result of the acute vascular injury. Platelets have been shown to be rapidly deposited in the form of a carpet overlying the injured vascular surface.[2] The deposition of platelets radiolabeled with indium 111 has also been noted at angioplasty sites, a process that was reduced with aspirin therapy.[3]

The mechanisms underlying more gradual coronary artery restenosis are not entirely clear but may involve the release of mitogens from platelets, contributing to smooth muscle cell proliferation and the synthesis of excess collagen.[4,5] Antiplatelet agents inhibit this process as well.

Major Clinical Trials

A retrospective study examined 300 consecutive patients who had angiograms done 30 minutes after angioplasty.[6] Patients either received no aspirin, aspirin with or without dipyridamole just before the procedure, or aspirin plus dipyridamole both before admission and in the hospital before PTCA. Antiplatelet therapy given both before admission and in the hospital effectively prevented immediate coronary thrombosis.

The Montreal Heart Institute Trial was a randomized, double-blind, placebo-controlled study in 376 patients undergoing coronary angioplasty in which patients received either placebo or aspirin, 330 mg, and dipyridamole, 75 mg three times a day, beginning 24 hours before PTCA.[7] Eight hours before the procedure, intravenous (instead of oral) dipyridamole was given at 10 mg per hour for the next 24 hours and oral aspirin therapy was continued. Sixteen hours after the procedure, the initial combination of therapies was reinstituted. Follow-up angiograms obtained in 249 patients four to seven months after the procedure showed that 38% of patients in the active therapy group had restenosis compared with 38.6% receiving placebo. There was a lower number of periprocedural Q wave myocardial infarctions in the group given the active drug, 1.6% versus 6.9% ($P = .011$). In a follow-up study, a secondary analysis showed that the severity of restenosis was greater in the group receiving a placebo than in the treatment group ($P = .01$).[8]

A recent study randomly allocated 216 subjects who were given aspirin for two weeks after PTCA to receive either 100 mg of soluble aspirin or placebo daily for the next six months.[9] At the end of the treatment period, restenosis had occurred in 25% of the aspirin-treated patients and 38% of the placebo-treated patients ($P < .05$). The loss of luminal diameter was significantly less in the aspirin-treated patients.

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ABBREVIATIONS USED IN TEXT

INR = international normalized ratio
PTCA = percutaneous transluminal coronary angioplasty
TIA = transient ischemic attack

Alternative Therapies

Seven trials have examined the possible therapeutic benefit of n-3 (ω-3) fatty acids in preventing restenosis after angioplasty.[10-16] Four of these have suggested efficacy of therapy, whereas three did not. The studies varied substantially in design and have been recently reviewed.[17] In general, the results have suggested a mild to moderate beneficial effect on restenosis. Two large multicenter trials of purified n-3 fatty acids currently underway may help clarify the issue.

Recommendations

- Aspirin, 325 mg, should be given at least one day before PTCA. In addition, a second dose should be administered an hour before the procedure. Heparin should be given throughout the procedure.
- Aspirin should be given at a dose of 325 mg daily thereafter. Aspirin therapy does appear to substantially reduce the rate of restenosis, although the degree of luminal reduction may be decreased. Long-term aspirin therapy can be recommended for the secondary prevention of cardiovascular disease.

Antiplatelet Therapy for Atrial Fibrillation

Rationale

Patients with chronic nonrheumatic atrial fibrillation have a high risk of thromboembolic events. For example, the risk of ischemic stroke is about five times that in patients in normal sinus rhythm. Cerebrovascular accidents occur at a rate of 3% to 8% of patients per year who have atrial fibrillation.[18]

Antiplatelet therapy might be effective for preventing thromboembolism in patients with atrial fibrillation because platelets may be involved in the formation of thrombi in the atria due to altered blood flow. In addition, there may be structural abnormalities of the mitral valve or other sites within the heart that could serve as a stimulus to platelet reactivity and that could respond to antiplatelet therapy.[19]

Major Clinical Trials

The Copenhagen Atrial Fibrillation, Aspirin, Anticoagulation Study (AFASAK) was a prospective, controlled trial involving 1,007 patients with chronic nonrheumatic atrial fibrillation in which the use of high-intensity warfarin sodium (international normalized ratio [INR]* 3 to 4.5) was compared with that of low-dose aspirin, 75 mg per day.[20] This trial included a relatively large number of older subjects and patients with advanced heart disease. In this trial, warfarin, but not aspirin, was effective in reducing embolic events over the subsequent two years.

The recently reported Stroke Prevention in Atrial Fibrillation study from the United States was a randomized, placebo-controlled trial of antithrombotic therapy in 1,330 patients with intermittent or constant atrial fibrillation that targeted ischemic stroke and systemic embolization as the primary outcome events.[22,23] Patients received warfarin at moderate intensity (INR 2.5 to 3.5), 325 mg per day of aspirin, or placebo. During a mean follow-up of 1.3 years, primary event rates were reduced by 42% in patients given aspirin ($P = .02$) and by 67% in patients eligible for warfarin treatment ($P = .01$). There appeared to be no benefit of aspirin therapy in patients 75 years of age or older. Because the aspirin- and warfarin-treated groups cannot be directly compared, a second trial now underway is specifically examining both the efficacy and the bleeding rates of aspirin versus warfarin therapy.

The Stroke Prevention in Atrial Fibrillation investigators have recently published two reports of subgroup analyses in the trial of antithrombotic therapy for nonrheumatic atrial fibrillation.[24,25] Several clinical variables—recent congestive heart failure, a history of hypertension, and previous arterial thromboembolism—were each associated with an increased risk of thromboembolism in the patients receiving placebo (>7% per year, $P \leq .05$). If patients lacked these clinical findings, the risk of thromboembolism was 2.5% per year. If one risk factor was present, the rate was 7.2% per year, and if two or three risk factors were present, then the rate was 17.6% per year. Additional information was provided by transthoracic echocardiography. Both left ventricular dysfunction and left atrial enlargement were strong predictors of subsequent thromboembolism.

The Boston Area Anticoagulation Trial for Atrial Fibrillation was an unblinded, randomized, 2.2-year controlled trial of low-dose warfarin therapy versus placebo in 420 patients with atrial fibrillation.[26] Patients in the control group were allowed to choose whether or not to take aspirin. Low-intensity warfarin therapy (INR 2.0 to 3.0) was associated with a significant 86% reduction in the risk of stroke. Aspirin was used by 46% of patients in the control group. A subgroup analysis of these patients by "treatment received" suggested that warfarin therapy was more effective than taking aspirin in preventing stroke.[27]

Recommendations

- Patients with chronic nonrheumatic atrial fibrillation should be treated with either aspirin, 325 mg per day, or low- to intermediate-intensity warfarin, at an INR of 2.0 to 3.0. Patients with recent congestive heart failure, hypertension, or previous arterial emboli are at an especially high risk of thromboembolism. Further studies are necessary to determine whether the use of warfarin will prove to be superior to that of aspirin in this group of patients.

*The INR is a standardized method of reporting prothrombin times to ensure that a uniform intensity of anticoagulant therapy is used worldwide.[21]

• Patients older than 74 years with chronic atrial fibrillation pose a special problem. Oral anticoagulant therapy may be slightly more effective than taking aspirin, but rates of intracranial bleeding may also be higher.[28] Elderly patients who cannot take anticoagulants may still benefit from aspirin, if only for the possible prevention of other cardiovascular disease.

• Patients with chronic atrial fibrillation who are at low risk of embolization—that is, no history of congestive heart failure, hypertension, or past emboli—and who have normal echocardiograms do not require treatment with antithrombotic agents. The use of low doses of aspirin, however, should be considered given its relatively low risks.

• Patients having had a previous cardioembolic event, including stroke, should probably be treated with oral anticoagulants rather than aspirin, until further data are available.

Antiplatelet Therapy for Patients With Artificial Cardiac Valves

Rationale

Platelets have been shown to adhere to paravalvular structures and prosthetic materials used for heart valve replacement.[29] In patients with mechanical heart valves, platelet survival as measured using radioactive chromium has been shown to be decreased in direct relation to prosthetic surface area and increased thromboembolic risk. Moreover, platelet inhibitors have been shown to normalize platelet survival in patients with prosthetic heart valves.[29]

Major Clinical Trials

As many as seven clinical trials that used a combination of dipyridamole with oral anticoagulants have shown that this combination of antiplatelet and anticoagulant therapy was superior to using warfarin alone for the prevention of thromboembolism (reviewed by Israel and coworkers[29]). When aspirin therapy (500 to 1,000 mg) has been combined with oral anticoagulants, however, the rate of major hemorrhage—patients requiring admission to a hospital or transfusion—has been significantly increased.[30] There have been few published trials using aspirin or dipyridamole therapy alone without concomitant oral anticoagulants in patients with mechanical heart valves.

In a trial reported several years ago by Sullivan and colleagues, a regimen of dipyridamole, 400 mg per day, plus warfarin substantially reduced the incidence of systemic thromboembolism compared with using warfarin alone in 163 patients with prosthetic heart valves.[31] After a year, arterial emboli developed in 13.9% of the warfarin-treated group compared with 1.3% of the patients receiving warfarin plus dipyridamole. Death rates were not different in the two groups.

Turpie and associates studied the effects of high-intensity warfarin therapy (INR 3.0 to 4.5) with aspirin (100 mg of a sustained-release preparation) or no aspirin in a group of 370 patients with mechanical prosthetic valves or high-risk tissue valves.[32] Patients receiving combination therapy had fewer major systemic emboli (2.7%) than did the group treated with warfarin alone (7.1%, $P = .04$). The incidence of major hemorrhage was similar in each group (12.9% versus 10.3%, not significant), although total (major plus minor) bleeding was higher in the group receiving warfarin plus aspirin (32.7% versus 26.1%, $P < .01$).

Recommendations

• Patients with mechanical artificial heart valves should receive oral anticoagulants as soon as possible postoperatively and be maintained at an intermediate-intensity range (INR 2.5 to 3.5).[33]

• Patients considered to be at an increased risk of thromboembolism—that is, having a history of embolization—can be given dipyridamole, 100 mg four times a day, in addition to warfarin.

• Large doses of aspirin when given in conjunction with high-intensity warfarin therapy have been shown to lead to a substantially increased risk of serious hemorrhage. Rates of major hemorrhage with smaller doses of aspirin, such as 100 to 160 mg a day, when administered with warfarin may be lower, and combination therapy may be considered in selected high-risk patients.

• If patients experience hemorrhagic complications with high-intensity warfarin therapy, then lower intensity anticoagulation (INR 2.5 to 3.5) plus antiplatelet therapy with dipyridamole should be considered.

• If warfarin therapy is absolutely contraindicated, then antiplatelet therapy might be considered using aspirin with dipyridamole or sulfinpyrazone. Alternatively, valve replacement with a bioprosthesis may be required.

• Platelet inhibitor therapy has not been adequately studied in patients with bioprosthetic heart valves, but aspirin, 325 mg per day, could be administered if patients are unable to tolerate oral anticoagulants. It is not known whether aspirin or warfarin use is more effective in patients with tissue valves who have chronic atrial fibrillation.

Primary Prevention of Stroke

Rationale

Although some acute cerebrovascular accidents may be caused by brain hemorrhage or cardioembolism, most are related to atherosclerosis. For example, of all strokes in subjects observed prospectively for 26 years in the Framingham Study, 57% were found to be atherothrombotic in origin.[34] Antiplatelet agents might be effective for the prevention of stroke by decreasing platelet emboli from ulcerated atherosclerotic plaques located in carotid arteries or other sites, such as the ascending aorta.[35,36]

Major Clinical Trials

The Physicians' Health Study showed that although physicians taking 325 mg of aspirin every other day had a 44% lower incidence of myocardial infarction, the incidence of stroke was higher (relative risk 1.22) but did

not reach statistical significance.[37] These strokes were mainly hemorrhagic in origin.

The British Doctors' Trial showed no significant difference in the rate of either myocardial infarction or stroke in subjects taking aspirin compared with no antiplatelet therapy.[38] The incidence of strokes that were defined as disabling was increased in the aspirin-taking subjects, however ($P = .05$).

In the Second International Study of Infarct Survival, hemorrhagic stroke developed in only 5 of 4,250 patients receiving both streptokinase and aspirin for acute coronary artery occlusion, and no hemorrhagic strokes were reported in a similar number of patients who received 160 mg of aspirin per day.[39] In the overall trial, aspirin therapy significantly reduced all incidences of nonfatal stroke from 0.6% to 0.3%, a difference that was statistically significant.

In the Antiplatelet Trialists' Collaboration Report, aspirin therapy was noted to significantly reduce the incidence of stroke in a meta-analysis of patients with manifest coronary artery disease.[40] If the trial entry criterion was cerebral disease—transient ischemic attack (TIA) or stroke—then the incidence of nonfatal stroke was reduced by 22%. If the trial entry criterion was cardiac disease, then the incidence of nonfatal stroke was reduced by 40%. Finally, if either disease was the entry criterion, the incidence of nonfatal stroke was reduced by 27%.

In a nonrandomized Nurses' Prospective Cohort Study, there was no alteration in the risk of stroke in those women who took aspirin (relative risk 0.99).[41]

Recommendations

- Antiplatelet therapy with aspirin, 325 mg a day or every other day, can be recommended for the primary prevention of stroke in patients who have documented coronary artery disease.
- Asymptomatic patients younger than 50 years who have no cardiovascular or cerebrovascular risk factors should not be given aspirin for the prophylaxis of thromboembolic stroke.
- Men older than 50 years who have coronary risk factors such as hyperlipidemia, diabetes mellitus, or hypertension should probably take aspirin at a dose of 325 mg every other day, mainly to prevent coronary artery disease. It is currently unclear whether the rate of thromboembolic stroke may be reduced by antiplatelet therapy in this group of patients or whether there may be a small increase in the rate of hemorrhagic stroke.

Secondary Prevention of Stroke After Transient Ischemic Attack

Rationale

The development of a transient ischemic attack or minor stroke confers a significant risk for the development of subsequent stroke or other vascular disease.[34] Because TIAs are thought to arise from platelet thromboemboli originating in carotid or cerebral vessels, antiplatelet therapy might be effective in these patients.[42]

Major Clinical Trials

An early double-blind trial reported by Fields and coworkers in 1977 studied 178 patients with TIAs who were treated with aspirin or placebo for 37 months. The results suggested that taking aspirin significantly decreased the incidence of stroke or vascular death after six months of therapy (odds ratio 0.47, $P < .01$), although no differences were found after 24 months of treatment.[43] Moreover, no significant differences were seen in the primary end point of combined TIA, death, stroke, or retinal infarction. If a subgroup of patients who entered the trial with multiple TIAs was considered, then aspirin therapy was found to be effective ($P < .05$).

The Canadian Cooperative Study Group reported a double-blind randomized study of therapy using aspirin, sulfinpyrazone, both aspirin and sulfinpyrazone, or placebo in 585 subjects with transient ischemic attacks.[44] After 26 months of treatment, aspirin therapy was associated with a significant reduction (relative risk 0.48, $P < .01$) in the end points of stroke and death in men. The risk of stroke and death in women was not significantly reduced, although this study was not designed to detect gender responses to treatment.

A double-blind randomized trial reported in 1983 by Bousser and colleagues compared the use of aspirin, 1 gram, plus dipyridamole, 225 mg per day, with placebo in patients with transient ischemic attacks or minor stroke.[45] After three years, aspirin therapy significantly reduced the rate of fatal and nonfatal cerebral infarction ($P < .05$). In addition, the rate of myocardial infarction was significantly ($P < .05$) reduced in the two treatment groups. No additional benefit was found when dipyridamole was added to the aspirin therapy.

The United Kingdom TIA Study Group published the results of a double-blind trial that randomly allocated[46] patients to receive either high-dose aspirin at 1,200 mg per day, low-dose aspirin at 300 mg per day or placebo.[47,48] After four years, no difference was observed between the low- and high-dose aspirin groups, but the use of aspirin in either dose significantly reduced a combined end point of stroke, myocardial infarction, or death when compared with placebo (odds ratio 0.85). There were no differences between men and women.

The European Stroke Prevention study was a large multicenter, randomized, double-blind, placebo-controlled trial involving 2,500 patients who had had a TIA, reversible ischemic neurologic defects, or completed stroke. Patients were treated with aspirin, 330 mg three times a day, plus dipyridamole, 75 mg three times a day, or placebo and were studied for two years.[49] Treatment with aspirin plus dipyridamole was associated with a 34% reduction in the incidence of the primary end point of stroke or death from all causes ($P < .01$), with similar findings in men and women. If TIA was the qualifying event for entry into the study, then a 44% reduction in end points was seen.

The Ticlopidine Aspirin Stroke Study was a prospective, randomized, blinded trial of ticlopidine hydrochloride, 500 mg daily, versus aspirin, 1,300 mg daily, in

3,069 patients with recent transient or mild persistent focal cerebral or retinal ischemia.[50] After three years, the rate of nonfatal stroke or death was 17% for ticlopidine and 19% for aspirin, a 12% risk reduction that was small but significant ($P = .05$). The incidence of the secondary end points of fatal or nonfatal stroke was further reduced by ticlopidine as compared with aspirin (odds ratio 0.79, $P = .02$). Ticlopidine therapy was associated with a higher incidence of cholesterol elevation, diarrhea, and neutropenia than was the use of aspirin.

A meta-analysis of seven randomized controlled trials comparing the use of aspirin with or without sufinpyrazone or dipyridamole with taking placebo was reported for patients with TIA.[51] For aspirin use compared with placebo, a nonsignificant reduction of 15% in the stroke incidence was found. When aspirin was combined with sulfinpyrazone or dipyridamole, an improved odds ratio of 0.61 ($P < .05$) was observed.

Two trials have been published that examined the effects of low doses of aspirin in patients after cerebrovascular ischemic events. The first of these, the Dutch TIA Trial, assessed the effects of 30 mg a day versus 283 mg a day of aspirin in 3,131 patients with a history of TIA or minor stroke.[52] After a 2.6-year follow-up, there was no difference in the frequency of death from vascular causes, nonfatal stroke, or nonfatal myocardial infarction (odds ratio for the lower dose of aspirin, 0.91). Fewer episodes of bleeding, gastrointestinal symptoms, and other adverse effects were seen with the 30-mg dose of aspirin.

The Swedish Aspirin Low-dose Trial (SALT) randomly assigned 1,360 patients with a history of TIA or minor stroke to receive either aspirin, 75 mg daily, or placebo, with a mean duration of follow-up of 32 months.[53] Patients receiving aspirin showed a reduction in stroke incidence or death of 18% compared with the placebo group (relative risk 0.82, $P < .05$). The aspirin-treated patients had a slight increase in the incidence of gastrointestinal side effects and a significant excess of bleeding episodes ($P < .05$).

Recommendations

- Aspirin, in doses of 30, 75, or 325 mg per day, should be administered to all patients with documented transient ischemic attacks or minor stroke. The lower doses of aspirin may reduce but not eliminate risks of excessive bleeding.
- Although ticlopidine may be an effective alternative therapy for patients who cannot tolerate aspirin, its use is associated with higher costs, frequency of administration, and rate of side effects.
- Anticoagulant therapy is not recommended for patients with TIAs, except for those who have chronic atrial fibrillation. As previously mentioned, it is not yet clear whether warfarin or aspirin therapy will prove superior in high-risk patients with atrial fibrillation.
- Patients found to have severe degrees of carotid artery stenosis—70% to 99%—should be considered for surgical endarterectomy (discussed later).

Secondary Prevention of Stroke in Patients With Completed Stroke

Rationale

Recurrent thrombotic cardiovascular events are common in patients who have suffered a completed stroke, and cumulative mortality is high.[34] The pathogenesis of recurrent stroke may involve the formation of platelet thromboemboli, which may be amenable to therapy with antiplatelet agents.

Major Clinical Trials

Several antiplatelet agents including sulfinpyrazone, suloctidil, and aspirin have not been effective in preventing recurrent stroke, myocardial infarction, or death in patients who have had a completed stroke.[54-56] Sufficient numbers of patients have been included in these trials to ensure that a risk reduction of 50% has not been missed but cannot guarantee that a risk reduction of 25% has not been missed.[57]

The Canadian American Ticlopidine Study was a double-blind, randomized trial of ticlopidine, 250 mg twice a day, versus placebo performed in 1,072 patients who had treatment started 1 to 16 weeks after having a completed stroke.[58] The combined primary outcome measure of recurrent stroke, myocardial infarction, or vascular death was assessed after a mean follow-up of two years. An analysis of the three end points showed a relative risk reduction with ticlopidine use of 30.2% ($P < .01$). Benefits were similar in both men and women. Adverse events (severe but reversible) associated with ticlopidine included neutropenia (1%), skin rash (2%), and diarrhea (2%).

Recently a subgroup analysis was done in patients enrolled in the Ticlopidine Aspirin Stroke Study who had a recent (within three months) minor completed stroke as the qualifying ischemic event.[59] In subjects who received 250 mg of ticlopidine twice a day, the cumulative rate of fatal or nonfatal stroke was 4.8% at one year compared with 7.5% for those receiving 650 mg of aspirin twice a day. This represented a risk reduction of 36% for ticlopidine relative to aspirin ($P = .20$). If the primary end point was nonfatal stroke or death, the rates were 6.3% and 10.8%, respectively ($P = .06$). The rate of adverse reactions was similar in both groups.

The European Stroke Prevention Study included 2,500 patients who had qualifying diagnoses of transient ischemic attacks, reversible ischemic neurologic defects, or stroke.[49] Patients were treated for two years with aspirin, 990 mg daily, plus dipyridamole, 225 mg daily, or placebo. Treatment was associated with a 33.5% reduction in stroke incidence or death from any cause ($P < .01$). If only patients with an entry criterion of completed stroke were included in the analysis, the risk reduction was 32.3%.

The Antiplatelet Trialists' Collaboration performed a meta-analysis using a total of 31 randomized trials of antiplatelet therapy in patients with vascular disease.[40] In those patients who presented with either TIA or com-

pleted stroke, antiplatelet therapy was associated with a reduction of 22% in the incidence of any subsequent vascular event. Unfortunately, the report did not distinguish between those patients who presented with TIA and those with stroke.

Recommendations

- Central nervous system benefits from the use of aspirin remain unclear in patients with completed stroke, but aspirin therapy, 325 mg per day, may be effective in preventing stroke and other cardiovascular disease.
- Based on a single study, ticlopidine may be an effective alternative to aspirin in patients who have had a stroke, but the higher cost of therapy and rate of adverse reactions including neutropenia must be considered.
- Anticoagulant therapy is not recommended for patients with completed stroke, unless there are other indications for treatment such as atrial fibrillation or severely impaired left ventricular function.

Antiplatelet Therapy for Patients Undergoing Carotid Endarterectomy

Rationale

Patients with carotid atherosclerosis treated by surgical endarterectomy remain at a high risk for recurrent cardiovascular events. For example, the combined rate of stroke, myocardial infarction, or death after carotid endarterectomy has been estimated to be about 12% over the next two years.[57] Many of these disorders may be mediated by platelet thromboemboli.

Radiographic studies using indium 111-labeled platelets have found marked deposition of platelets at the endarterectomy site immediately after operation.[60] In one study, the treatment of patients with aspirin and dipyridamole led to significantly decreased [^{111}In]platelet deposition at the operative site.[61]

Major Clinical Trials

A small double-blind trial of aspirin, 1,300 mg per day, versus placebo in patients undergoing carotid endarterectomy was reported by Fields and colleagues.[62] Patients were treated within five days of the surgical procedure and observed for at least six months. Two patients in the aspirin group had stroke or died compared with four patients in the placebo group, yielding an odds ratio of 0.44 in favor of aspirin therapy.

In a subsequent trial reported in 1988, 301 survivors of carotid endarterectomy were randomly allocated to receive either low doses of aspirin, 50 to 100 mg per day, or placebo starting within 1 to 12 weeks of the operation.[63] Aspirin doses were titrated to maximally inhibit ex vivo platelet aggregation. After a mean treatment duration of 25 months, the incidence of the clinically important combined outcomes of stroke, myocardial infarction, or vascular death was not different in the two groups (odds ratio was 1.1).

Kretschmer and associates published both a retrospective and a prospective clinical trial of antiplatelet therapy in patients having a carotid endarterectomy.[64] Antiaggregating drugs were reported to prolong patient survival in the retrospective study ($P << .01$). In the prospective trial, 66 patients were recruited, with half receiving aspirin, 1,000 mg a day, and half receiving no therapy. During follow-up, 15 patients died, 4 in the treatment and 11 in the control groups ($P < .02$).

The North American Symptomatic Carotid Endarterectomy Trial was a large (659-patient) multicenter study that randomly allocated patients with 70% to 99% carotid artery stenosis to surgical or medical therapy.[65] All patients received antiplatelet therapy—1,300 mg of aspirin a day. At two years, the cumulative risk of total ipsilateral stroke was 26% in the medical patients and 9% in the surgical patients, a risk reduction of 17% ($P < .01$). Similar reductions were observed for severe or fatal ipsilateral stroke.

The European Carotid Surgery Trial randomly assigned 2,518 patients to surgical or medical treatment.[66] For 374 patients with only mild (0% to 29%) stenosis, there was little risk of ipsilateral stroke in either group. In the 778 patients with severe stenosis (70% to 99%), however, the risk of ipsilateral stroke beginning a month after the operation and for the next three years was 2.8% for surgical patients compared with 16.8% for medical patients ($P << .01$). In this study, aspirin therapy was recommended, but not required, in both groups of patients.

A third multicenter study was recently published by the Veterans Affairs Cooperative Study Group in which 444 male patients with asymptomatic carotid stenosis of 50% or more were randomly assigned to optimal medical treatment (including aspirin, 650 mg twice a day) or to carotid endarterectomy plus optimal medical treatment.[67] The surgical group had a combined incidence of ipsilateral neurologic events of 8% compared with 20.6% in the medical patients (relative risks 0.38, $P < .001$). There were no differences in the combined end point of all strokes and deaths (relative risk 0.92). Most of the deaths were due to coronary atherosclerosis.

A recently published trial compared the use of aspirin, 325 mg, plus dipyridamole, 75 mg three times a day, in 83 patients undergoing carotid endarterectomy with that of placebo in 80 patients.[68] Therapy in the actively treated group was started 12 hours before the operation. There were no differences in the incidence of restenosis found in the aspirin-plus-dipyridamole group, and rates were even somewhat higher in those receiving antiplatelet therapy.

Recommendations

- Symptomatic patients with high-grade carotid artery stenosis should be referred for surgical endarterectomy if they have access to a highly qualified surgical team. The results of one clinical trial of antiplatelet therapy following carotid endarterectomy have now been published and suggest that antiplatelet therapy is of no benefit in preventing restenosis. Low-dose aspirin therapy, however, such as 325 mg daily, can be recommended in an effort to prevent cardiac or other vascular disease.
- Patients with lesser grade stenosis, if they are not

enrolled in a clinical trial, should be treated with low-dose aspirin, 325 mg per day, until the results of clinical trials are available for these groups of patients.

- Aspirin therapy has not been effective in patients with high-grade carotid artery stenosis who are not candidates for surgical treatment. The optimal antithrombotic therapy for this group of subjects is unknown.

Chronic Lower Extremity Ischemia

Rationale

Graft occlusion occurs frequently in patients with saphenous vein and bioprosthetic arterial grafts.[69] A substantial proportion of thromboses developing in small-caliber arterial bypass grafts in humans may be platelet mediated. For example, studies in primates have shown that platelet deposition occurs in external bioprosthetic grafts, which can be reduced by antiplatelet therapy.[70,71] In addition, at least 90% of patients requiring surgical intervention for chronic lower extremity ischemia have angiographically demonstrable coronary artery disease, an important additional indication for the use of antiplatelet agents.[72]

Major Clinical Trials

Four randomized prospective trials of antithrombotic therapy in patients with peripheral artery bypasses were recently reviewed.[69] Two small studies found a statistically significant reduction in the incidence of prosthetic bypass occlusion with antithrombotic therapy. In these studies, therapy with aspirin plus dipyridamole was started preoperatively. In a larger study, however, when antithrombotic therapy was begun postoperatively, no significant difference between the groups was observed.

In a more recent study, 140 patients receiving femoral distal bypass grafts were randomly allocated to receive either placebo or dipyridamole, 200 mg twice a day, for 48 hours preoperatively and then dipyridamole plus aspirin, 300 mg daily, for six weeks after the operation.[73] After one year, there was a higher patency rate found in the treated group ($P = .01$) that was entirely accounted for by the patients receiving prosthetic rather than vein grafts. The patency rate was 85% in the patients with prosthetic grafts versus 53% in the control group ($P < .01$). The beneficial effect was observed during the first postoperative month.

More recently, a large multicenter trial from England showed that there was no improvement in the patency of saphenous vein femoral or tibial grafts when patients were treated with aspirin and dipyridamole.[74] In this study, 549 patients were recruited to a randomized double-blind trial comparing the use of aspirin, 300 mg, plus dipyridamole, 150 mg twice a day, with that of placebo. Therapy was started two days before the operation. Despite the lack of benefit on vein graft patency, the antiplatelet therapy significantly reduced the incidence of myocardial or cerebral infarction over the next 34 months ($P < .01$).

A randomized, prospective, multicenter trial using dextran 40 was conducted in patients undergoing a lower extremity bypass procedure.[75] Dextran was infused during the operation and for three days afterward. There was substantially increased patency in the dextran-treated patients in the first week of the operation, but after one month no significant differences were found. The subgroup of patients who had prosthetic bypasses or long distal bypasses appeared to benefit most from treatment.

Alternative Therapy

The results of a small but prospective, randomized controlled trial in 88 patients suggested that oral anticoagulant therapy reduced the incidence of thrombotic occlusion of reversed saphenous vein-femoral popliteal bypass grafts by about 50% after 2½ years of follow-up ($P < .03$).[76] Of interest, a longer follow-up of this group of patients suggested that overall mortality was also reduced with oral anticoagulant treatment ($P < .02$).[77] When patients who suffered vein graft occlusions were excluded from the analysis, the difference in probability of survival remained significant ($P < .01$). A ten-year follow-up showed continued benefit on graft patency, limb salvage, and survival.[78]

Recommendations

- Antiplatelet therapy is recommended for patients undergoing infrainguinal arterial bypass and in patients with chronic lower extremity ischemia being treated nonoperatively. For optimal protection, antiplatelet therapy should be begun preoperatively and should consist of aspirin, 325 mg per day.
- Another alternative is administering dextran 40 during and immediately after the operation. Therapy with aspirin, 325 mg per day, should be started postoperatively a day or two before the dextran is discontinued.
- For long-term antithrombotic therapy, one tablet of aspirin daily with or without dipyridamole can be recommended, although it is not clear that the dipyridamole is necessary. Although it is uncertain whether the use of aspirin will modify the natural history of peripheral vascular insufficiency, these patients are at high risk of future cardiovascular events (stroke and myocardial infarction), and lifelong treatment with aspirin should be considered.
- Warfarin sodium is an alternative to antiplatelet therapy, especially in patients with prosthetic grafts that extend below the knee or in patients with thrombotic failure of previous bypass grafts.

Future Strategies for Antiplatelet Therapy

As exemplified by many of the clinical trials cited here, antiplatelet therapy has improved dramatically, and this progress should continue. New therapeutic possibilities include combining two antiplatelet agents with differing mechanisms of action or adding antiplatelet agents to oral anticoagulants or fibrinolytic agents to improve therapeutic efficacy without unacceptable rates of bleeding. A wide variety of innovative antiplatelet agents are now being developed and tested.[79] Examples include

monoclonal antibodies and specific inhibitory peptides to block glycoprotein IIb-IIIa binding sites on platelets, agents that inhibit glycoprotein Ib to reduce platelet adhesion, and potent low-molecular-weight antithrombins that prevent the aggregation of platelets and the formation of fibrin. It is hoped that this research will result in more effective antithrombotic therapy for patients with occlusive vascular disease.

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Epitomes

Important Advances in Clinical Medicine

General and Family Practice

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in general and family practice. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in general and family practice that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General and Family Practice of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Estrogen Replacement Therapy for Reducing Cardiovascular Disease

ESTROGEN REPLACEMENT THERAPY has been widely advocated and accepted for use in preventing osteoporosis in postmenopausal women. Yet, a more important effect may be its ability to decrease the incidence of cardiovascular disease in these women. Whereas premenopausal women have myocardial infarctions at a rate much lower than that of men of the same age, the rate of myocardial infarction in women in the first ten years after menopause approaches that in men. Myocardial infarction becomes the leading cause of death in women older than 50.

At least 16 prospective studies have reviewed the effects of exogenous estrogen on the risk of myocardial infarction. The Nurses' Health Study, which observed 121,700 married female registered nurses for ten years, established a 44% reduction in the risk of coronary artery disease for those women on estrogen replacement therapy. The Lipids Research Clinic study observed more than 2,000 women for nine years, and the death rate for cardiovascular disease for women on estrogen replacement therapy was a third of that for women not receiving therapy. The protective effect of estrogen replacement was not modified by smoking, alcohol use, obesity, or high blood pressure.

The exact mechanism by which estrogen replacement provides protection to postmenopausal women is not well understood. Estrogen does have a favorable effect on serum lipid profiles by increasing high-density lipoprotein (HDL) levels while decreasing total cholesterol and low-density lipoprotein levels. Women in the Lipids Research Clinic study had HDL levels 9 to 12 mg per dl (0.23 to 0.31 mmol per liter) higher than did nonusers. Reviewing data from the Framingham and the Lipid Research Clinic studies suggests that an increase in HDL levels of about 10 mg per dl (0.26 mmol per liter) is associated with a 50% to 60% decrease in cardiovascular risks. Other hypotheses for the protective effect of estrogen therapy include a reduction of endothelial hyperplasia and atherosclerosis, in addition to an enhanced production of prostacyclin.

When considering estrogen replacement, it is important to balance the risks versus the benefits of therapy. Whereas estrogen is definitely associated with endometrial cancer and an increased incidence of gallbladder disease, its relationship to breast cancer is controversial. In contrast to the use of oral contraceptives, estrogen replacement has not been associated with an increased incidence of venous thrombosis, thrombophlebitis, or pulmonary embolism. In addition, some studies have shown that postmenopausal estrogen replacement does not raise systolic or diastolic blood pressure in normotensive or hypertensive women.

Absolute contraindications to estrogen replacement therapy include acute liver disease or previously diagnosed breast or endometrial cancer. Relative contraindications include chronic liver disease, obesity, and a history of thromboembolism.

The possible benefits and risks to the cardiovascular system associated with the addition of progesterone to estrogen replacement have not been clearly defined. Although progesterone has been shown to decrease HDL levels, a recent study indicates that women using both estrogen and progestin had the same reduction in cardiovascular risk factors as women using estrogen only. On the other hand, another study reported that while the sequential use of estrogen and progestin had a favorable effect on the lipid profile, the effect was less than that of using estrogen alone. Any possible effect of progestins on cardiovascular risk is likely to be related to the dose and duration of the therapy.

Estrogen replacement has long been advocated for the prevention and treatment of osteoporosis. Newer infor-

mation indicates that it may have an even more important role in preventing life-threatening cardiovascular disease. The protective nature of estrogen on the cardiovascular system should provide a strong impetus for lifelong therapy. By educating and encouraging patients to consider estrogen replacement therapy, physicians may substantially contribute to a reduction of the risk of cardiovascular disease in their postmenopausal women patients.

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Sleeping Position and Sudden Infant Death Syndrome

THE SUDDEN INFANT DEATH SYNDROME (SIDS) is defined as the sudden and unexpected death of an infant in whom a thorough postmortem examination does not show an adequate explanation for death. It is the leading cause of death for infants beyond the perinatal period to 12 months of age. The peak incidence of sudden infant death is from 2 to 4 months of age; 80% of cases occur before age 5 months. Two of 1,000 infants die of SIDS. African Americans and Inuits appear to be at the greatest risk for SIDS and Asians and whites at the least risk.

Epidemiologic studies have identified the following risk factors for the syndrome: prematurity, birth weight low for gestational age, low Apgar scores, inadequate prenatal care, low socioeconomic status, mother younger than 21 years, mother using illicit drugs during pregnancy, and siblings died of SIDS. Several studies have recently reported a striking association between SIDS and sleeping in the prone position. A study from Avon County, England, found a relative risk of 8.8 for sleeping in the prone position. This same study found overheating (by clothing and bedding) to be an independent risk factor for sudden infant death. Studies from the Netherlands and Australia have corroborated this association between SIDS and sleeping prone.

Following the discovery of this association, health care professionals in Avon County altered their advice on sleeping position for infants, recommending instead the side or supine positions—except in infants with chronic gastroesophageal reflux or certain congenital deformities, such as the Pierre Robin syndrome. A follow-up study found that the prevalence of prone sleeping fell from 58% to 28% and the incidence of SIDS fell from 3.5 per 1,000 to 1.7 per 1,000.

The reason for the association between the prone sleeping position and SIDS is unknown, but some researchers have shown the likelihood of suffocation by rebreathing expired air in infants sleeping prone on certain types of infant bedding, particularly those that are excessively soft and malleable.

The pathophysiology of SIDS remains a riddle. Primary care physicians should encourage their patients to receive prenatal care and forego smoking and drug abuse. Current research suggests that physicians should counsel parents to avoid "bundling" infants with excessive clothing and blankets and to recommend placing infants without contraindications in the supine or side positions to sleep.

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Outpatient Management of Asthma

PRIMARY CARE PHYSICIANS have been asked to help reduce the morbidity and mortality of asthma in the 1990s. In response to the almost 30% rise in asthma prevalence and mortality between 1980 and 1987, the expert panel of the National Asthma Education Program has issued guidelines to improve the detection and treatment of asthma.

Asthma is a chronic condition with acute exacerbations. It is now considered an inflammatory disease in which bronchospasm occurs because of airway inflammation. Treatment requires a continuous care approach to control symptoms, prevent exacerbations, and reduce chronic airway inflammation. The education program's guidelines place emphasis on anti-inflammatory therapy through the use of inhaled corticosteroids and inhaled cromolyn sodium as first-line therapy for moderate to severe asthma.

Clinicians must use objective measures of pulmonary function, such as a home peak-flow meter, to assess and monitor each person's asthma. With appropriate pharmacologic therapy, environmental control, and education, patients and their families can achieve control of this condition. Just as people with diabetes mellitus on insulin therapy can monitor their blood glucose levels at home, patients with asthma can objectively monitor their condition by measuring peak expiratory flow rates at home. By taking regular measurements, patients with moderate to severe asthma can prevent severe exacerbations by early intervention. Measurements are obtained at 7 AM and 7 PM each day, as well as before and after the inhalation of bronchodilators. When the peak expiratory flow rate is between 80% and 100% of the patient's personal best, no changes are needed. When it drops to between 50% and

80% of personal best, a temporary increase in medication is needed. When the peak expiratory flow rate falls to less than 50% of baseline levels, bronchodilators are used immediately and the patient's physician notified if the rate does not rise at once and stay at higher levels.

In severe exacerbations, airflow obstruction needs to be rapidly reversed. In young, otherwise healthy people with asthma, emergency department or office treatment initially involves inhaled β-agonists every 20 to 30 minutes, up to three doses. This closely spaced regimen for acute exacerbations produces incremental bronchodilation with each successive inhalation. The use of parenteral corticosteroids is recommended if the patient's symptoms fail to resolve after this treatment.

Patient education has moved to the forefront of outpatient asthma management. Those skilled in self-management can achieve some control over their lives and their condition. It has been shown that early treatment is most effective. Home management of acute exacerbations avoids delays in initiating therapy. Patients require instruction on the correct use of medications, and the use of spacers with inhaled medications often augments this. Patients with moderate to severe asthma should keep diaries to record home peak expiratory flow rates and to document symptoms. All patients should have a written action plan to be followed in the event of an acute exacerbation. Each person's optimal management strategy evolves over time and benefits from the objective data offered by home measurements of peak expiratory flow rates.

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Practical Approach to Diagnosing and Treating Sinusitis

SINUS DISEASE is one of the most prevalent chronic diseases causing widespread morbidity and economic hardship, and yet it is one of the most difficult diseases to diagnose with objective criteria.

The following types of recurrent episodes of sinus-associated symptoms indicate the need for a more detailed diagnostic workup: symptoms that interfere with daily living, episodes recurring more than three to four times per year, symptoms that are not controlled by nonpharmacologic measures (such as steam inhalations or saline-solution sprays) or over-the-counter medications, more than one anatomic site in addition to the sinuses are affected by symptoms (ears, teeth, eyes, or brain), and sinus disease being associated with other problems (such as exacerbations of asthma).

The workup of patients with these symptoms may include plain sinus radiographs. Sinus films are helpful in patients with maxillary sinusitis in whom there is evidence of sinus mucosal thickening greater than 6 mm, but they are not helpful in the diagnosis of ethmoid sinusitis. Computed tomography is currently the diagnostic test of choice to diagnose recurrent sinusitis. It is crucial to request coronal sections with bone-window settings of the ostiomeatal complex. Limiting the scan to this region will focus the scanner on the most likely pathologic area and also reduce the cost of the study to $100 to $200 per scan. Fibrotic rhinoscopy, done by a skilled practitioner, can help locate abnormalities, such as nasal polyposis or subtle changes in lymphoid tissues, in the posterior nasal passages and nasopharynx. Allergy skin testing is appropriate only if the history is consistent with allergic disease—seasonal exacerbations, exacerbations to specific environment exposures, worsening asthma, and so on.

If chronic disease is found, the following medical regimen should be instituted. A broad-spectrum antibiotic—amoxicillin, 500 mg three times a day, or the combination of trimethoprim and sulfamethoxazole, double strength, twice a day—should be prescribed for a minimum of 21 days. In children and recalcitrant adult cases, the combination of amoxicillin and clavulanate potassium should be used to treat *Moraxella (Branhamella) catarrhalis* infection. Patients should receive topical nasal corticosteroids—beclomethasone dipropionate, flunisolide, or budesonide—to decrease ostial inflammation and increase the sinus ostial diameter to enhance sinus drainage. High-dose guaifenesin and oral α-adrenergic agonists should be given to thin respiratory secretions and to increase ostial patency, respectively. An attempt should be made to promote continued sinus drainage after symptoms resolve. Saline solution and steam can help liquefy secretions and increase mucociliary clearance, especially in the ostiomeatal complex. Finally, in chronic sinusitis where anatomic anomalies are the cause or soft tissue masses persist, surgical therapy is the best approach.

Because adequate objective criteria to diagnose this common ailment are not available, physicians need to rely on clinical intuition. It is important to note that other, less common, underlying causes of sinusitis need to be considered, including cystic fibrosis, immotile-cilia syndrome, and several immunocompromised states, in particular immunoglobulin A deficiency. In addition, undiagnosed and untreated sinusitis can be associated with severe, albeit rare, complications, such as subdural or epidural empyema (frontal sinus), brain abscess (frontal), meningitis, cavernous sinus thrombosis (sphenoid), osteomyelitis (frontal), and orbital cellulitis (ethmoid). Although sinus roentgenograms have been shown to have as high as a 40% false-negative rate, the lateral and Caldwell views may be helpful in diagnosing sphenoid, frontal, and ethmoid sinusitis. Finally, in resistant chronic sinusitis, not only is there an occasional indication for sinus aspiration and irrigation, but an initial

four- to five-day burst of oral steroid therapy, to decrease mucosal edema and encourage drainage, and antibiotic therapy, including cephalosporins (such as cefaclor) for as long as three to six weeks may be required for adequate treatment.

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Health and Medical Care of Homeless Persons

FAMILY PRACTITIONERS and general internists provide most of the health care to the 3 million homeless people in the United States. Recent studies have enhanced our ability to provide medical care to these people by delineating their health problems and the barriers to medical care that they face.

Homeless people are generally sicker than others. A third of homeless adults have chronic serious mental illness; the same proportion have substance abuse problems. A third of homeless children have developmental delay, and the same number are depressed. A third of homeless adults and half of homeless children have at least one physical illness. Diseases of the following organ systems predominate: upper respiratory, cardiovascular, dermatologic, female genitourinary, gastrointestinal, peripheral vascular, musculoskeletal, dental, and ophthalmologic. Homeless women have inadequate reproductive care, and only 30% use birth control. They are more than twice as likely as poor women with homes to be pregnant; more than half have inadequate prenatal care. In addition, they are twice as likely as poor women with homes to give birth to an infant with a low birth weight (16%), and they have twice the infant mortality rate (25 deaths per 1,000 live births).

Contagious disease is rampant among the homeless. In New York City, more than half of men at homeless clinics had a skin test positive for tuberculosis, and 45% were positive for the human immunodeficiency virus. Despite their high prevalence of illness, half of the homeless say that they did not obtain needed medical care in the previous year.

What should a practitioner do with this information? First, all impoverished patients should be assessed for their housing status. When the homeless do request medical care, they should be given a careful history, complete physical examination, and age- and sex-appropriate health screening. These patients should be assessed for mental health and substance abuse problems, physical and sexual abuse, dental health, and vision and podiatry problems. Appropriate immunizations should be administered, and homeless patients should be screened for tuberculosis.

To reduce homeless persons' barriers to care and compliance, health professionals should be sensitive to the problems of homelessness and trained to manage illness in persons who have no place to stay. Clinics need to be near areas where homeless people live. Walk-in clinic appointments and providing some medical care in outreach settings are essential. Simple and quick laboratory testing should be done in the office, but relationships should be established with local hospitals and laboratories to do more extensive diagnostic evaluations. Free medications available on-site would enhance compliance with a medical regimen. Given their many problems, primary care, mental, substance abuse, dental, optometry, and social services should be provided on-site or in nearby facilities. Transportation to referral sites may be required. Respite care might prevent hospital stays for problems that could be treated if a homeless patient had a home.

Most homeless persons will respond to medical treatment if it is provided in an atmosphere of trust and respect. It is difficult to attract physicians to centers that care for homeless people. Medical students' interest in caring for the poor would be fostered by exposing them to role models and clinical experiences that provide care to the homeless and other impoverished groups.

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Practice Guidelines Movement

"CLINICAL POLICIES," "practice guidelines," and "practice parameters" are synonyms for one of the current trends in medicine. Many clinicians resist this movement, fearing that the development of these policies will transform medical practice into nothing more than "cookbook medicine." Fears of medicolegal liability, the uncertain response of insurers, and confusing terminology intensify this resistance. What do these policies mean? What if two policies conflict? What if a clinician does not agree with the policy? These important questions can be addressed by reviewing the way guidelines are developed and ways to determine their flexibility.

More than 1,000 policies are either in place or under development. Many different groups, from federal agencies to specialty societies to private groups, continue to develop new policies. Clinical policies are preformed recommendations designed to help clinicians make decisions about the management of patients. Policies are not a new medical phenomenon; they are a classic method of disseminating information. Informal clinical policies include "treat strep throat with penicillin," "obtain a

yearly mammogram," "once a cesarean section, always a cesarean section," and other clinical pearls passed down through hospital rounds and textbooks. Popular examples of formal policies include the United States Preventive Services Task Force's *Guide to Clinical Preventive Services,* the cancer screening recommendations from the American Cancer Society, and the findings of any National Institutes of Health consensus conference. Any clinical policy—for example, the one on cesarean deliveries—may need modification when more data become available.

Clinical policies can be based on one of two approaches. In a consensus conference, experts meet to discuss the current state of knowledge. The evidence and exact rationale for the experts' recommendations are often obscure. More recently, an explicit approach has increased in popularity. This is important because the explicit approach allows clinicians to determine how to apply a policy to patients in their practice.

The explicit approach requires knowledge in three areas: all relevant health effects, including benefits and harms; all financial costs and savings; and patient preferences. Usually an extensive literature review serves as the source of all data, but occasionally new data are developed. Patient preferences for the various treatment options or outcomes are assessed. Finally, the data are formally analyzed and the recommendations published. The explicit approach, while resulting in high-quality recommendations, is expensive. Developing a high-quality policy generally takes thousands of hours over two to three years.

A scheme has been suggested for rating the flexibility of a clinical policy, that is, how strong the recommendation should be. A policy is a "standard" if the consequences are well known and there is virtual patient unanimity about the value of the recommendation. Few guidelines carry this strict level of flexibility. The policy on treating severe hypertension can be considered a standard. A policy is a "guideline" if the consequences are sufficiently understood to permit decisions and the recommendation is preferred by many but not all patients. The policy on mammography after age 50 years is a guideline. A policy is an "option" if the outcomes or patient preferences are not known or if patients are either evenly divided or indifferent. The policy on treating moderate hypercholesterolemia is considered an option because of the lack of data on patient preferences as well as current controversies over the possible adverse effects of lowering cholesterol levels.

The perceived rigidity of clinical policies causes many physicians to resist the entire movement, fearing that such rigidity will interfere with the patient-physician interaction. By incorporating a flexibility rating, however, these clinical policies offer physicians the latitude to use clinical judgment while identifying those recommendations with clear and powerful evidence. Certain potential concerns related to clinical policies are well founded, and the American Academy of Family Physicians is a leader in the field to help protect patients from the misuse of these policies by nonclinicians. Still, the comprehensive assessment of a clinical problem afforded by a clinical policy can give physicians insight into the optimal care of patients.

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Universal Hepatitis B Childhood Vaccinations

THE CENTERS FOR DISEASE CONTROL AND PREVENTION Immunization Practices Advisory Committee recommended universal childhood hepatitis B immunizations in November 1991. The initial reaction by physicians and the various professional societies was guarded, but most professional organizations have now made similar recommendations.

Hepatitis vaccine was introduced in 1982. Early hepatitis B vaccination efforts focused on high-risk populations. Despite these efforts, it is estimated that 200,000 to 300,000 new cases occur each year in the United States. Each year nearly 5,000 people die of chronic liver disease due to hepatitis B virus (HBV), and more than a million people have chronic infection and are potentially infectious to others. The immunization of high-risk groups will remain a cornerstone of efforts to control this disease until universal childhood immunization results in control.

Infants and children younger than 5 years have special risks related to HBV infection. Infants infected in the perinatal period have a 90% risk of chronic infection. Those not infected at birth from infected mothers remain at high risk for acquiring the infection. In addition, horizontal person-to-person transmission has been shown to occur among children in populations where HBV is endemic. Children infected in the first five years of life have as much as a 60% risk of becoming carriers. It is estimated that 25% of children with chronic HBV infection will die of chronic liver disease as adults.

Each person in the United States faces a 5% lifetime risk of HBV infection. This risk makes universal vaccination of infants probably cost-effective when comparing the cost of vaccine and its administration with the medical and work-loss costs associated with the disease. It has been estimated that each dollar spent on vaccination will save between $7 and $14 in medical and work-loss costs.

Several schedules have been recommended depending on the HBV status of the mother, the vaccine used, and individual vaccination practices. Generally half the adult dose (a fourth to half for Recombivax HB) is administered at birth (with hepatitis B immune globulin given if

the mother is HBV infected). The second dose is administered a month or two later, and the third dose four or more months thereafter to obtain optimal antibody levels. The question of the need for a booster dose is not resolved, but protective levels of antibody are present for at least five years. The possible need for booster doses will be assessed as additional information becomes available.

Effective December 1, 1992, and January 1, 1993, respectively, California and Nevada Medicaid programs began paying the costs of childhood hepatitis B vaccination.

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Increased Surgical Options for Dysfunctional Uterine Bleeding

HYSTERECTOMY FOR DYSFUNCTIONAL uterine bleeding remains a common and expensive treatment. Because 50% of the uteruses removed for this reason are histologically normal, techniques are being developed to treat the target tissue, the endometrium, rather than remove the entire organ.

Endometrial ablation has been studied for more than 100 years, but technologic improvements in the past 10 to 15 years have now shown consistent results with low morbidity. First, instruments for endometrial aspiration done in the office have shown results equal to those of dilatation and curettage in the diagnosis of endometrial carcinoma. Second, hysteroscopy now permits direct visualization of the endometrium to ensure thorough ablation. Third, laser or electrosurgical devices provide effective and safe ablation.

The laser techniques cauterize the endometrium while the procedure is viewed through the hysteroscope. A review of the results of different studies over the past decade involving more than 1,000 patients showed an 88% to 97% success rate, with failure being defined as requiring a subsequent procedure or a hysterectomy. Electrosurgical equipment such as a urologic resectoscope (such as used for transurethral resection of the prostate) or a roller-ball electrode may also be used. Both use electrical current to cauterize the endometrium down to the basement membrane. Several studies, with results from hundreds of patients, reported success rates of 86% to 97.5%. The resectoscope also gathers tissue for histologic study and can be used to remove small submucosal fibroids.

Endometrial ablations can be done as outpatient procedures with shorter recovery times than for hysterectomies. As their availability increases throughout the country, primary care physicians will be able to offer patients procedures that are less uncomfortable, disruptive, and costly than a hysterectomy when medical therapy is unsuccessful.

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Changing Guidelines for Screening Mammography

BREAST CANCER is the most common cancer among women in the United States with each year about 175,000 new cases diagnosed and 44,000 deaths. Recommendations for screening mammography in asymptomatic women are made with the goal of reducing mortality through early detection and intervention.

Since 1980, the American Cancer Society (ACS) in conjunction with the National Cancer Institute has recommended yearly mammography for asymptomatic women older than 50 years. Controversy has surrounded recommendations for screening women from 40 to 49 years. Concerns have included a marginal cost-benefit ratio and lack of data to support decreased mortality among younger women when cancer is found by mammography. Supporters of annual screening in this age group point to the relative aggressiveness of cancer that occurs in younger women.

In 1983, based on data from the joint ACS/National Cancer Institute Breast Cancer Detection Demonstration Project and long-term follow-up from the Health Insurance Plan of New York study, the ACS guidelines were revised to include screening mammography every one to two years from 40 to 49 years of age. At that time, the ACS also recommended a baseline mammogram for future comparison for women between ages 35 and 39.

Guidelines were again revised by the ACS and published in August 1992 after a consensus meeting of 12 health care organizations was convened by the American College of Radiology to develop a uniform set of recommendations for breast cancer screening. The new guidelines reconfirm the use of screening mammograms on a yearly basis for women older than 50 and every one to two years for women from 40 to 49 years old.

Not all organizations have endorsed the recommendations for screening women younger than 50 years. The United States Preventive Services Task Force does not endorse routine mammography for women aged 40 to 49 unless they fall into a high-risk category based on family history. The recently published five-year follow-up

results from the Canadian National Breast Screening Study do not show a decreased rate of death from breast cancer in the women from age 40 to 49 in the group screened by mammogram despite the increase in early detection.

The recommendation for a baseline mammogram at age 35 to 39 years has been deleted from the ACS guidelines.

Screening guidelines are intended to provide a uniform framework for health care professionals in which to recommend mammographic breast cancer screening for asymptomatic women. These recommendations are not static and may need to be revised in response to studies that clarify the effect of early detection and intervention on the natural history of breast cancer.

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Alerts, Notices, and Case Reports

Acute Dilated Cardiomyopathy as a Cluster in Children

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WE REPORT A CLUSTER OF six patients with severe dilated cardiomyopathy who were seen in our pediatric intensive care unit. All of the patients were from a similar geographic area, and all presented during the same two-month period from June through July of 1992. This represents a substantial increase in the normal incidence of dilated cardiomyopathy seen at our hospital, suggesting an infectious outbreak.

Report of Cases

Case 1

The patient, a 4-year-old girl from Banning, California, had been healthy but had an upper respiratory tract infection about two weeks before admission that lasted for a few days and then resolved. Four days before admission, diffuse abdominal pain developed, and the patient vomited several times. She was seen by her pediatrician two days before admission and treated with an oral electrolyte maintenance solution (Pedialyte) without relief. On the day of admission, periorbital and peripheral edema developed, and the patient was seen by her physician again. A chest radiograph showed cardiomegaly, pulmonary vascular congestion, and pleural effusions. The patient was referred to our pediatric intensive care unit for further management.

On admission, an echocardiogram showed normal cardiac anatomy, a small pericardial effusion, severe left ventricular dilatation, and severe left ventricular hypokinesis with an estimated fractional shortening of 3%. Following therapy,* the patient improved symptomatically but had transient bradyarrhythmias with noxious stimuli (intravenous catheter placement and venipuncture). The patient's cardiac function did not improve echocardiographically, and she was considered for cardiac transplantation.

*All of these patients, except for case 5, were managed with a regimen of intravenous inotropes including amrinone lactate and dobutamine hydrochloride for five to seven days. The patients also received intravenous furosemide, captopril, aspirin, and levocarnitine. All patients were placed on fluid restriction. When the inotropes were discontinued, all were started on oral digoxin therapy. Patient 3 received treatment with intravenous heparin followed by warfarin sodium.

(McConnell MS, Perkin RM, Hernandez R: Acute dilated cardiomyopathy as a cluster in children. West J Med 1993 May; 158:522-525)

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Case 2

The patient, a 6-month-old male infant from Barstow, was previously healthy but presented to a nearby emergency department after five days of increasing cough, wheezing, and respiratory difficulty. There was no antecedent fever, abdominal pain, rhinorrhea, nasal congestion, or change in feeding habits. The patient was admitted to the hospital and treated for asthma. On the following day a chest radiograph showed cardiomegaly and pulmonary edema. The patient was referred to our pediatric intensive care unit for further management.

Evaluation by echocardiogram showed normal cardiac anatomy with severe left ventricular dilatation, severe left ventricular dysfunction, moderate mitral regurgitation, and a left ventricular fractional shortening of 8%. The patient improved clinically, but repeated echocardiograms showed no improvement in left ventricular function. During the hospital course, the patient had repeated episodes of intermittent atrial fibrillation and flutter unresponsive to the administration of adenosine or digoxin but eventually controlled with intravenous procainamide hydrochloride. Cardiac catheterization revealed normal coronary arteries and left ventricular pressures of 100/30 mm of mercury. A metabolic workup of urine metabolic and organic acids, serum carnitine, lactate, and creatine kinase levels elicited values that were within normal limits. The patient is currently awaiting a heart transplant.

Case 3

The patient, a 14-year-old girl from Barstow, had a two-month history of intermittent chest pain, dyspnea, coughing, and occasional vomiting. She had been admitted to a nearby hospital in May 1992 and diagnosed with congestive heart failure. She was discharged and admitted again three more times with exacerbating congestive heart failure and treated with diuretics and digoxin. The patient was referred to our hospital for further management. At the time of admission, she was having intermittent chest pain, abdominal pain, and shortness of breath. The patient had a history of polydrug abuse including amphetamines.

Echocardiographic evaluation on admission showed normal cardiac anatomy with severe left ventricular dilatation and dysfunction, mild mitral regurgitation, a 2- by 3-cm thrombus in the left ventricular apex, and a left ventricular fractional shortening of 14%. The patient improved clinically without notable improvement in left ventricular function. Cardiac catheterization revealed a dilated left ventricle with an estimated ejection fraction of 25%, normal coronary arteries, and cardiac output of 3.5 liters per minute. A right ventricular biopsy showed moderate myocyte hypertrophy and mild focal interstitial fibrosis. The patient was discharged to home with close cardiologic follow-up.

TABLE 1.—*Differential Diagnosis of Dilated Cardiomyopathy in Children*

- Infectious (myocarditis)
  - Viral
  - Bacterial
  - Protozoan
  - Fungal
  - Rickettsial
  - Parasitic
- Coronary artery disease
  - Anomalous coronary artery
  - Kawasaki's disease
- Chronic tachydysrhythmias
- Drugs or toxins
- Metabolic
  - Hypoglycemia
  - Hypothyroidism or thyrotoxicosis
  - Pheochromocytoma
  - Defects in fatty acid oxidation
    - Carnitine deficiency
- Congenital heart disease
- Neuromuscular disorders
  - Duchenne type muscular dystrophy
  - Myotonic dystrophy
  - Limb-girdle muscular dystrophy
    - Erb's dystrophy
  - Friedreich's ataxia
  - Spinal muscular atrophy
  - Multiple lentiginosis
- Inborn errors of metabolism
- Endocardial fibroelastosis
- Genetic or familial
- Idiopathic dilated cardiomyopathy

Case 4

The patient, a 15-month-old female infant from Palm Desert, was healthy when, four days before admission, abdominal pain developed and she had decreased oral intake, lethargy, and weakness. Her symptoms worsened, and she had wheezing and respiratory difficulty. On the day of admission the patient was seen by her pediatrician, who diagnosed pneumonia. On the way home, the patient became apneic and cyanotic and was taken to a nearby emergency department where she was noted to have an agonal heart rate of 40 beats per minute. The patient received cardiopulmonary resuscitation and was intubated. A chest radiograph taken in the emergency department showed cardiomegaly and pulmonary edema. The patient was later transported to our pediatric intensive care unit.

An echocardiogram taken on arrival to our intensive care unit showed normal cardiac anatomy with a severely dilated left ventricle, severe left ventricular dysfunction, pulmonary hypertension, and moderate mitral regurgitation. The patient improved clinically, but a second echocardiogram showed no improvement in cardiac function and a left ventricular fractional shortening of 13%. She is currently being considered for a heart transplant. She has suffered neurologic sequelae from her respiratory arrest.

Case 5

A year-old male infant from Victorville had been healthy when, three weeks before admission, a slight cough developed that progressively worsened. A week before admission, he had increasing respiratory distress and was treated for asthma without relief. The patient was noted to have a decreased appetite and needed to rest after being active. He was admitted to the hospital for intravenous steroid and antibiotic therapy and for further respiratory care. A chest radiograph obtained after admission showed cardiomegaly and pulmonary venous congestion. An echocardiogram revealed a small pericardial effusion, a dilated left ventricle with poor systolic function, and a fractional shortening of 19%.

The patient was managed with oral digitalis, intravenous furosemide, and captopril with considerable symptomatic improvement. He was discharged to home in a stable condition with good exercise tolerance. The plan is to repeat the echocardiogram in the near future to assess left ventricular function.

Case 6

This patient is a 6-year old boy from Moreno Valley, with congenitally acquired immunodeficiency syndrome. He had been in his normal baseline state of health when a nonproductive cough and some respiratory distress developed. He was admitted to our hospital where culture of a sputum specimen grew *Streptococcus pneumoniae*. The patient was treated with intravenous antibiotics and discharged home on oral antibiotic therapy. The following week he had persistent coughing and the development of abdominal pain with an episode of vomiting without diarrhea. A chest radiograph revealed cardiomegaly with pulmonary vascular congestion. An echocardiogram showed a severely dilated left ventricle with left ventricular dysfunction and a shortening fraction of 4%. The child has improved clinically with little improvement in cardiac function.

Discussion

All of these patients presented with signs and symptoms of a severely dilated cardiomyopathy that did not improve substantially after treatment. The intriguing aspect of these cases is the proximity in time and location in which the patients presented, suggesting an infectious cause. Because not all of the patients underwent myocardial biopsies, some may argue that other causes (Table 1) have not been completely disproved. Patients 1, 2, and 4

had other causes for metabolic cardiomyopathies ruled out by specific laboratory testing. All patients had normal coronary artery anatomy verified by echocardiogram or cardiac catheterization. Patient 3 was originally considered to have a cardiomyopathy due to amphetamine or cocaine use, but the biopsy findings were not consistent with this source. Patient 5 was treated at another hospital, and no known metabolic workup was pursued. Patient 6 certainly has other factors that could cause a dilated cardiomyopathy, including infection with the human immunodeficiency virus and treatment with zidovudine (known to cause cardiomyopathy), but the abrupt onset of his symptoms argues for an acute infection. In all of these patients, except patient 3, idiopathic dilated cardiomyopathy cannot be completely dismissed from the differential diagnosis without doing a myocardial biopsy. Nonetheless, the clinical presentation and the fact that these cases occurred in a similar geographic area and in the same time period argue strongly for an outbreak of infectious myocarditis, likely caused by a virus.

All of these patients lived in Riverside or San Bernardino county in or near desert areas (Figure 1). A review of admissions to our pediatric intensive care unit for the past five years revealed an average of only two to three

Figure 1.—The map shows the towns in San Bernardino and Riverside counties, California, where the 6 children with acute dilated cardiomyopathy lived.

cases per year of dilated cardiomyopathies, but all six of these patients presented during a two-month period in the summer of 1992. Larger outbreaks and epidemics of viral myocarditis have been reported.[1-3] Many such cases, however, are asymptomatic or subclinical infections, which makes the task of identifying a large outbreak arduous. In addition, a multitude of viruses are known to cause myocarditis (Table 2), making serologic identification of the causative agent difficult at best. The current methods of identifying viral pathogens include culturing stool, urine, pharyngeal, and myocardial specimens—although the recovery of viral agents remains unreliable and delayed.[2,4,5] Viruses can be identified by virus-specific immunoglobulin M in the host. Other methods currently being developed include fluorescent antibody stains directed against replicating viruses in myocardial specimens and direct fluorescent antibody probes obtained from other host sites.[6] To date we have not been able to culture any specific virus from specimens obtained from these patients.

TABLE 2.—*Viral Agents That Cause Myocarditis*

Adenoviruses	Herpesviruses
Arboviruses	Herpes simplex
Chikungunya	Varicella
Coxsackie virus A (many strains)	Influenza A and B
Coxsackie virus B (many strains)	Measles
Cytomegaloviruses	Mumps
Dengue	Poliovirus
Echoviruses	Rabies
Hepatitis viruses	Rubella
	Vaccinia

The diagnosis of myocarditis is usually suggested by the results of a routine history and physical examination. Patients may or may not have had a preceding upper respiratory tract infection followed by increasing respiratory distress, lethargy, decreasing oral intake, and abdominal pain. The physical examination may demonstrate tachypnea, tachycardia, retractions, wheezing or rales, a heart murmur or gallop, hepatomegaly, weak pulses with delayed capillary refill, peripheral edema, and cyanosis. Further diagnostic inquiry should include a chest radiograph, which shows cardiomegaly (with a cardiothoracic ratio of greater than 0.5) and bilateral alveolar infiltrates. An electrocardiogram may reveal sinus tachycardia with ST segment abnormalities, T wave inversions, and arrhythmias. An echocardiogram will demonstrate left ventricular dilatation with left ventricular dysfunction and a reduced fractional shortening.

As evidenced by these case descriptions, dilated cardiomyopathy due to myocarditis can be devastating even with prompt and appropriate treatment. All too often, however, the diagnosis is delayed because of the protean symptoms. Patients are also often misdiagnosed with pulmonary disease or abdominal disease, further delaying appropriate treatment. Pediatricians, emergency physicians, family practitioners, and other clinicians should be made aware of this possible outbreak of viral myocarditis and keep a high index of suspicion in children presenting with abdominal pain or respiratory distress. Further public health investigation is being pursued in Riverside and San Bernardino counties to assist in identifying this apparent outbreak of myocarditis.

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Cytomegalovirus-Induced Thrombocytopenia in an Immunocompetent Adult

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THROMBOCYTOPENIA is an infrequent yet well-recognized complication of viral infection. Mumps, rubella, varicella, and infectious mononucleosis have each been documented to cause thrombocytopenia.[1] But although thrombocytopenia has been commonly observed in patients with congenital cytomegalovirus (CMV) infection,[2] it has rarely been reported after CMV infection in immunocompetent adults. We describe a case of profound thrombocytopenia that occurred ten weeks after a primary CMV infection.

Report of a Case

The patient, a 31-year-old man, was seen because of sore throat for five days that was followed by a week of malaise, headache, loss of appetite, night sweats, and fever. He had no history of illnesses that would cause an immunodeficient state, and he had no risk factors for infection with the human immunodeficiency virus. The patient was previously in good health, was not receiving any medications, and had no history of transfusions or drug or alcohol abuse. On physical examination he had a temperature of 38.5°C (101.3°F) and a spleen palpable 1 cm below the costal margin. Laboratory tests revealed a leukocyte count of 5.2×10^9 per liter (5,220 per μl), with 0.57 neutrophils, 0.24 lymphocytes (including many atypical forms), 0.08 bands, 0.06 monocytes, 0.04 eosinophils, and 0.01 basophils. The hemoglobin level was 145 grams per liter (14.5 grams per dl), and the platelet count was 137×10^9 per liter (137,000 per μl). A prothrombin time, partial thromboplastin time, and erythrocyte sedimentation rate were normal. Blood chemistry

(Eisenberg MJ, Kaplan B: Cytomegalovirus-induced thrombocytopenia in an immunocompetent adult. West J Med 1993 May; 158:525-526)

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TABLE 1.—*Cases of Thrombocytopenia After Cytomegalovirus (CMV) Infection in Immunocompetent Adults*

Source	Age, yr	Sex	Presentation	Interval	Platelet Count, $\times 10^9$/liter	Diagnostic Tests	Treatment and Results
Chanarin and Walford, 1973[5]	33	M	General purpura and gingival bleeding	3 wk after onset of illness	5	Titers 1:1,024 to 1:4,096; CMV cultured in urine	Prednisone, 60 mg/day for 3 wk and then tapered; platelet count, 139×10^9/liter by day 16
Fiala and Kattlove, 1973[6]	18	M	Confluent purpura, gingival bleeding, and petechiae	Several weeks after onset of infection	2	Positive IgM test; CMV cultured in buffy coat and urine	Prednisone, 120 mg/day for 16 days, then vincristine sulfate, 2 mg, followed by splenectomy on day 25; no response; prednisone therapy restarted; normal platelet count by day 46
Harris et al, 1975[7]	27	M	Ecchymoses and petechiae	Beginning day 6 of illness	18	Titers 1:16 to 1:1,024; positive IgM test	Prednisone, 60 to 100 mg/day for 2 wk; little response; steroids tapered as CMV titers declined; platelet counts normal by 1 mo
Sahud and Bachelor, 1978[8]	21	M	Shoulder pain, petechiae, and buccal hemorrhages	No preceding illness	12	Titers 1:1,024 to 1:16 after 3 mo	Refractory to high-dose steroids (persistent thrombocytopenia at 7 mo); bone marrow examination findings consistent with ITP; splenectomy; normal platelet count after several days
Shimm et al, 1980[9]	20	M	Petechiae, gingival bleeding, and prolonged bleeding with shaving	No preceding illness	<10	Diagnosed as ITP by bone marrow examination	Refractory to high-dose steroids; splenectomy at 7 wk; platelet count returned to normal
			Fever, scattered petechiae	4 wk after splenectomy	38	CMV cultured in blood	Normal platelet count in 1 wk without treatment

IgM = immunoglobulin M, ITP = idiopathic thrombocytopenic purpura

ABBREVIATIONS USED IN TEXT

CMV = cytomegalovirus
Ig = immunoglobulin

values were also normal, with the exception of the lactate dehydrogenase (334 U per liter, normal 100 to 260), aspartate aminotransferase (70 U per liter, normal 7 to 40), and alanine aminotransferase (85 U per liter, normal 6 to 45). A chest roentgenogram was unremarkable, and both blood and urine cultures were sterile. Paul-Bunnell and Weil-Felix tests were negative, as was serologic testing for *Brucella* species, Q fever, the Epstein-Barr virus, *Salmonella typhi*, and *Haemophilus parainfluenzae*. An immunoglobulin (Ig) M titer was strongly positive for CMV, and there was a fourfold increase in IgG titers over two weeks (from $<1:20$ to 1:80); CMV was later identified in the urine.

Four weeks after the symptoms started, the patient felt well. A hemogram and blood chemistry values were normal. After ten weeks, he noted easy bruisability and rectal bleeding. On examination he had ecchymoses over the lower extremities and scattered petechiae over the upper back. The platelet count was 13×10^9 per liter, the hemoglobin was 151 grams per liter, and the leukocyte count was 7.8×10^9 per liter. A regimen of prednisone, 40 mg per day, and aminocaproic acid, 3 grams per day, was begun. There was a modest increase in the number of platelets at one week, and aminocaproic acid was discontinued shortly thereafter. At the end of three weeks, the platelet count was only 36×10^9 per liter. The prednisone dosage was doubled to 80 mg per day for two weeks and was subsequently tapered after the platelet count reached 52×10^9 per liter. The prednisone therapy was discontinued after 11 weeks, and the platelet count stabilized at 113×10^9 per liter after four months.

After three years of follow-up, the patient continues to be in good health. Platelet counts have always been higher than 100×10^9 per liter.

Discussion

Infection with CMV is known to cause a number of potentially life-threatening conditions in immunocompetent persons, including pneumonia, myocarditis, encephalitis, and the Guillain-Barré syndrome.[3] In patients with the acquired immunodeficiency syndrome, CMV infection may have additional manifestations, most notably retinitis and colitis. Although thrombocytopenia has been seen in patients with the acquired immunodeficiency syndrome who have CMV infections,[4] CMV-induced thrombocytopenia in immunocompetent adults appears to be rare, with only five previous cases having been reported (Table 1).[5-9]

Because CMV-induced thrombocytopenia has been reported so rarely in immunocompetent adults, it is difficult to know the natural course of this disease. In four of the previously reported cases, symptomatic thrombocytopenia became evident within several weeks after the onset of infection.[5-7,9] In the fifth case, the time course was unclear because the patient had only serologic evidence of a previous CMV infection.[8] There were various responses to steroid treatment ranging from no response to normal platelet counts in two weeks. In addition, platelet counts often returned to normal as CMV titers declined, so it is difficult to know whether steroid therapy was of benefit. Splenectomy appeared to be useful in the two patients in whom idiopathic thrombocytopenic purpura was diagnosed,[8,9] but in the one patient in whom splenectomy was done specifically for CMV-induced thrombocytopenia,[6] there was no response.

The mechanism by which CMV induces thrombocytopenia is unknown, but two have been proposed: a direct cytopathic effect on megakaryocytes and an immune-mediated effect.[9] The distinction may have important therapeutic implications because an immune-mediated effect would be expected to respond to steroids but a cytopathic effect would not. In our patient, platelet counts were near normal for at least four weeks after the onset of infection, and symptomatic thrombocytopenia became evident only ten weeks after the onset. This temporal relationship suggests that an immune-mediated mechanism was responsible; a direct cytopathic effect of the virus would be expected to be evident much sooner in the clinical course.

The long latent period we observed also raises two clinical questions: Is asymptomatic thrombocytopenia a frequent occurrence after CMV infection? and are CMV infections responsible for some cases of thrombocytopenia that are misdiagnosed as idiopathic thrombocytopenic purpura? From the case we report, we conclude that for patients with acute CMV infection, a platelet count should be determined if there is evidence of petechiae, purpura, or bleeding, and for patients presenting with idiopathic thrombocytopenia, it may be worthwhile to examine for evidence of a previous CMV infection.

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Commentary

Human Immunodeficiency Virus in India
Reflections of a Visitor

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A "health disaster." A "time bomb." This was my impression of the human immunodeficiency virus (HIV) in India from journal and newspaper articles and discussions with experts in the United States. A "flash in the pan." "Your disease, not ours." Empty AIDS [acquired immunodeficiency syndrome] wards. These were my first glimpses of the situation as I began eight months of work and studies in India last year.

As a fourth-year medical student at the University of California, San Francisco, I traveled to southern India in the fall of 1991 to join an HIV epidemiology group. I met clinicians, researchers, and policymakers around the country working with HIV. I wanted to see a country at a different point on the epidemic curve, to think about what social forces would influence the shape of the curve, and to investigate how a conservative culture would respond to the urgent need for AIDS education.

My time was divided between research and clinical rotations. I spent four months initiating a screen for HIV in a government tuberculosis hospital in Madras, in collaboration with HIV epidemiologists at the Christian Medical College, Vellore. For the next three months I worked in Vellore, concluding research as well as beginning clinical rotations in community and inpatient medicine. In my final month I did a medicine rotation at the All India Institute of Medical Sciences in Delhi. Throughout my visit I questioned physicians, students, and even Rotarians about their knowledge of and attitudes towards HIV.

Epidemiology

The population of India unofficially tops 1 billion. The life expectancy at birth is 54.4 years, the infant mortality rate is 104 per 1,000, and the death rate 11.7 per 1,000. Per capita income is approximately $133 a year. India spends about 3% of its gross national product on health and family welfare. There is one physician for every 2,610 persons, but up to 80% of physicians are concentrated in urban areas that account for only 20% of the population. As of 1987 only 14,400 of 23,000 planned primary health centers had been established. The HIV epidemic only adds to the major health problems of the country, which include communicable diseases such as malaria, filaria, tuberculosis, diarrheal disease, and leprosy; malnutrition; environmental sanitation; and population growth.[1]

As of December 1991, more than 1.2 million people had been screened for HIV; 6,319 were seropositive.[2] Of these, 48% were classified as "heterosexually promiscuous"; 21% were intravenous drug users; 15% professional blood donors; 2% blood product recipients; and 0.1% homosexuals. Prevalences within the high-risk groups screened were as follows: heterosexually promiscuous, 1.95% (n = 153,009); blood donors or blood product recipients, 0.20% (n = 539,641); intravenous drug users, 38.4% (n = 3,521); others (including anonymous screening in hospital clinics and volunteer testing), 0.17% (n = 509,984). Estimates of the number of HIV-infected persons range between 250,000 and 1 million.

Although only 102 cases of AIDS have been reported in India, the World Health Organization estimates that the actual number is between 2,700 and 9,000.[2]

National AIDS Control Program

Since 1985 the government of India has worked to keep abreast of the spread of HIV and to direct funds toward personnel training and technological support. As outlined in government publications, their national program to control AIDS has several arms.[2]

- *HIV Testing.* India has established 62 surveillance centers, where enzyme-linked immunosorbent assay (ELISA) screening is done, and 7 referral centers that are capable of performing Western blot testing. The central government provides an unlimited supply of ELISA testing kits. Researchers at major centers have been screening patients in sexually transmitted disease clinics since 1985; periodically, other high-risk groups such as prostitutes or truck drivers are targeted. Rates of 30% in prostitutes in Bombay[3] and more than 50% in intravenous drug users in Manipur[4] have been reported. Ongoing screening in antenatal, medical, and surgical clinics in at least two centers (Madras and Vellore) will provide valuable information about the rate at which HIV is entering the general population.
- *Clinical Care.* The government has designated 13 hospitals as AIDS referral centers, with four already

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equipped. Physicians and nurses have been sent to the United States and Australia for training in clinical diagnosis, management, and infection control. Programs to train a physician from each major city, designated as a PRAD [physician responsible for AIDS diagnosis], are in the development stage.

• *Blood Safety.* India currently has 1,018 blood banks, 20% of which are private and for-profit. Through increased funding of the 128 testing centers and the creation of new centers, the long-term goal is to screen 80% of all blood handled.

• *Health Education and Information.* Under this broad category, the government plans to use mass media, printed material, and voluntary organizations for AIDS education and to develop a condom promotion campaign.

India has recently received major international funding for its AIDS control program: an $84 million loan from the World Bank; $14.1 million from the government of India; and $1.5 million from the World Health Organization.[5] The money is intended to strengthen existing infrastructure: a third for blood safety; a third for education and a condom program; and a third for sexually transmitted disease control, HIV surveillance and research, and program management.

Health Care for Patients Infected With HIV

Government statistics barely reflect the reality in the rapidly evolving field of caring for HIV-infected persons. The premier AIDS ward at the All India Institute of Medical Sciences in New Delhi was empty during the six weeks I was there. In contrast was the busy and unique HIV clinic at the Christian Medical College of Vellore, a large missionary hospital in rural southern India not even listed as an official treatment center. This clinic cares for 150 seropositive patients and has diagnosed 32 cases of AIDS. Unlike the atmosphere of disinterest and misinformation about HIV in the Indian medical community as a whole, this hospital's staff members are responding to the challenge of HIV.

The clinic at the Christian Medical College, held one afternoon a week, is run by a dermatologist—in India, HIV is categorized as a sexually transmitted disease, and these diseases are treated by dermatologists—an internist, and a psychiatrist. Asymptomatic patients are seen every three months; every six months blood, stool, and urine laboratory examinations are done. A detailed questionnaire recently implemented will generate information on risk factors for infection and the clinical course of HIV disease in infected persons.

Patients are initially unwilling to attend clinic. To some, a diagnosis of HIV is a stigma, certain to be misunderstood by family, employer, and landlord. To most, however, the diagnosis of a chronic disease that may not affect them for years is of small concern. These patients are bewildered at the degree of attention paid to them and, like most patients, are reluctant to give up a day's wage or bus fare to visit the hospital even if they have medical problems. Although the clinic may see only 10 to 15 patients a day, it is clearly capable of handling the inevitable rise in number of HIV-infected and AIDS patients.

According to the Madras physician credited with identifying the first case of HIV in India in 1985, private hospitals are refusing to treat AIDS patients, and patients are reluctant to go to public hospitals because of publicity. Her innovative solution is to train 25 former prostitutes infected with HIV to provide home care for terminal AIDS patients. The area of the country most in need of clinical support is the northeastern region, a remote area bordering Burma. In contrast to the rest of India, the concern here is drug use: in the major state in the region, Manipur, there are an estimated 15,000 intravenous drug users, 50% of whom are HIV-positive.[4] Numerous Indian and foreign consultants have traveled to this tribal region to assess the situation, but no major diversion in clinical personnel or funds has been initiated by the government.

In this area and in major cities throughout India, there is also the acute need for drug treatment and counseling services as part of HIV transmission-reduction efforts. According to the government of India, the first four counselors have just been trained to cover the northeast region.[2] In Bombay, a city with an estimated 400,000 addicts, there are 8 counselors; in all of India there are only 160 counseling centers and 30 "de-addiction" centers (M. Irani, "Sitting on a Time Bomb," *Sunday Times of India,* June 27, 1992). Along with health education efforts, drug counseling and rehabilitation services need to be high priorities.

Response of the Medical Profession

As I traveled to meet various clinicians who had treated HIV-infected patients, I expected to hear stories of a lack of resources. I was not surprised, for example, that no patient with AIDS has been diagnosed with *Pneumocystis carinii* pneumonia; not only is the incidence in these patients probably less in developing countries, but laboratories are not equipped and technicians not trained to make this diagnosis. I was not prepared, however, for the apathy shown by most of the clinicians I met. In India AIDS is considered a sexually transmitted disease, relegated to dermatologists who are low in status in the medical hierarchy. Indian physicians feel the incidence in India is too low for concern or even that it is nonexistent—I spent an afternoon in a sexually transmitted disease clinic of a major Madras teaching hospital arguing with physicians who refused to believe there are any cases of HIV infection in India. I attended a conference in chest medicine where the first two papers reporting HIV prevalence in tuberculosis patients were presented—and watched the hall empty and the remaining crowd grow restless during the presentations. There are many other major diseases demanding the attention of Indian physicians, but the number of AIDS cases predicts that soon enough HIV will affect every specialty.

Another factor that contributes to the apathy is that physicians at this point have seen only two snapshots of

the AIDS epidemic: patients screened in the clinic who are HIV-positive and well and patients, critically ill and in the hospital, suspected of and tested to be HIV-positive. Some physicians think there is a high false-positive rate of ELISA in India and do not believe test results in their healthy patients. Most physicians I met, however, conclude from the two disparate pictures that HIV infection does not necessarily lead to AIDS. Only more experience treating HIV-infected patients and emerging case reports in the Indian literature will demonstrate clearly that AIDS is in India and is a terminal disease.

Health Education and Nongovernmental Organizations

The challenge to educate a billion people about AIDS is overwhelming, but the goal is attainable. Recent studies in Ghana and Zaire show near-universal knowledge about AIDS following major educational campaigns.[6,7] Few studies have been done in India to assess knowledge about HIV. The literate may have some awareness of the disease through newspapers and magazines, but knowledge about transmission and prevention are lagging far behind. A survey of 153 English-speaking Indians in Calcutta found awareness of AIDS in 93%, but only 5% knew that condoms are protective (S. B. Porter, MD, PhD, unpublished data, 1991). The rural and illiterate are not receiving the message. A study done in Vellore found awareness of AIDS in 42% of a primarily rural population.[8] As part of my work I interviewed 90 patients, again primarily rural and illiterate; 36% of men and 5% of women had heard of AIDS.

Although there are frequent newspaper articles on AIDS, printed patient education materials are almost nonexistent, primarily because of a lack of funds. Although the government is mandated to spend 35% of the World Bank loan on health education, there is no stated systematic plan for how the media will be used.[2] There is no indication that the AIDS education scheme will coordinate with the existing family planning education program, nor are there any specifics on condom promotion. Historically, the government, physicians, and community health workers have favored permanent over temporary means of contraception as a more efficient tool for population control. A politically and socially sensitive issue, it will take major work within the bureaucracy before condoms are distributed freely and effectively in India.

As in other countries, nongovernmental organizations are evolving to fill the health education gap. In Madras the AIDS Action Program has been instrumental in developing innovative programs for villages and inner cities, such as folk plays and puppet shows. Video vans, already in use for family planning education, are being developed. The videos feature current film stars and are combinations of song and dance sequences from films and health education blurbs. Other projects of the AIDS Action Program include an upcoming health camp, including HIV screening, for truck drivers. Most of these activities are only in the major cities of Madras and Bombay, however.

It is not difficult to become alarmed by the attitude of physicians or overwhelmed by the number of obstacles to health education in India. These obstacles are as large as widespread female illiteracy and government bureaucracy and as manageable as a lack of funding for fleets of video vans or a lack of progressive counselors to speak openly about condoms. Creative approaches, as well as lessons learned in other countries, are needed to avoid the "health disaster" that indeed looms.

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Editorials

Overcoming the Limitations of Chemotherapy in the Treatment of B-cell Non-Hodgkin's Lymphomas—An Approach Using Radiolabeled Peptide Ligands

THE TREATMENT OF CANCER has changed rapidly over the past 20 years. Previously incurable malignant neoplasms, such as germ cell tumors, thyroid cancers, leukemias, lymphomas, and early breast and colon cancer, now can be cured with combined modalities including surgical therapy, radiotherapy, and chemotherapy. The value of chemotherapy in the adjuvant setting has been shown in stage B2 and C colon carcinomas, in rectal carcinoma, in breast cancer, and in ovarian germ cell tumors. Promising palliative therapy is available for prostate cancer, small-cell lung cancer, colon cancer, and sarcomas.[1]

Although advances in the treatment of lymphoma were made in the 1970s with the introduction of combination chemotherapy such as CHOP (cyclophosphamide, doxorubicin hydrochloride [formerly hydroxyldaunomycin], vincristine sulfate [Oncovin], and prednisone),[2] and MOPP (mechlorethamine hydrochloride, vincristine, procarbazine hydrochloride, and prednisone),[3] little progress has been made in the past 15 years. Lymphomas are treated according to patients' overall health, the clinical stage, and the tumor grade at presentation, with grade defined by the National Cancer Institute's Working Formulation as low, intermediate, or high.[4]

To date, most low-grade non-Hodgkin's lymphomas are incurable. Two separate philosophies have prevailed in the treatment of low-grade lymphomas: aggressive therapy at the time of diagnosis versus watch and wait, reserving therapy for bulky, rapidly progressive disease or disease compromising vital functions, such as ureteral obstruction or bone marrow suppression. A study at the National Institutes of Health showed that there was no difference in long-term survival if aggressive chemotherapy was given at the time of diagnosis or at a later point.[5] The survival curves are similar to those obtained at our own institution (Stanford University Medical Center, Palo Alto, California), where we treat patients with a watch-and-wait approach, followed by less intensive chemotherapy consisting of cyclophosphamide, vincristine, and prednisone or chlorambucil. It remains to be seen if high-dose chemotherapy with autologous bone marrow rescue has a role in the treatment of low-grade lymphomas. While the response rates are high, the procedure-related mortality is about 10%, and early reports show relapses occurring following autologous bone marrow transplantation. This procedure should be reserved for the experimental setting.

In contrast, the therapy for intermediate- and high-grade lymphomas is based on combination chemotherapy given with or without radiotherapy with a curative intent. Complete response rates of 66% for stages III and IV disease with long-term survival rates of less than 30% were achieved with CHOP in the 1970s.[2] In the 1980s, the development of second- and third-generation regimens, such as M-BACOD (methotrexate, bleomycin sulfate, doxorubicin [Adriamycin], cyclophosphamide, vincristine sulfate [Oncovin], and dexamethasone),[6] MACOP-B (methotrexate, Adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin),[7] or ProMACE-CytaBOM (prednisone, methotrexate with leucovorin rescue, Adriamycin, cyclophosphamide, etoposide [UP-16], cytarabine, bleomycin, and vincristine)[8] were shown to be more effective in single institution trials. A randomized multi-institutional trial of these four regimens, reported in abstract form,[9] showed no advantage of the three newer regimens over CHOP in outcome, but showed increased toxicity for MACOP-B and M-BACOD. Autologous bone marrow transplantation appears to have a role in the treatment of relapsed intermediate- and high-grade lymphomas, at least when the results are compared with those of historical controls. It remains to be tested further as a first-line therapy in newly diagnosed high-risk patients. The treatment of patients with intermediate-grade non-Hodgkin's lymphomas can be rewarding for the approximately 50% of patients who can be cured, whereas little progress has been made since the introduction of CHOP in 1976 for patients in advanced stages or those for whom the primary therapy fails.

It is possible that we have reached the limits of chemotherapy in the treatment of lymphomas. It is not clear that intensifying the dose will significantly improve current cure rates. Novel treatment strategies will need to be developed. In his article elsewhere in this issue, Kit Lam, MD, PhD, proposes to develop a therapy based on peptides, which are small proteins.[10] He plans to use them to deliver radiation therapy to lymphoma cells, comparable to the delivery of a bomb with a cruise missile programmed to hit a specific target. The difficulty lies in developing a peptide that will specifically attach to tumor and not to other cells. Lam intends to exploit the immunoglobulin receptor unique to the tumor of each patient (idiotype). If a peptide could be found that binds to the idiotype of the tumor with a high affinity, the peptides could be administered intravenously. Circulating in the blood, they would attach to immunoglobulin receptors bearing that particular idiotype. The unattached peptides would be excreted in the urine. If the peptide were labeled with radioactivity, the cells to which the peptides bound, as well as the surrounding cells, would receive radiotherapy.

The concept of using a specific molecule to target a receptor dates back to 1900, when Paul Ehrlich postulated that antibodies could be used as "magic bullets" for cancer therapy.[11] Since then, scientists have developed antibodies directed against a variety of tumor-associated antigens.[12] They have used them alone, relying on the

ABBREVIATIONS USED IN TEXT

CHOP = cyclophosphamide, doxorubicin hydrochloride (formerly hydroxyldaunomycin), vincristine sulfate (Oncovin), and prednisone
MACOP-B = methotrexate, doxorubicin (Adriamycin), cyclophosphamide, vincristine, prednisone, and bleomycin
M-BACOD = methotrexate, bleomycin sulfate, doxorubicin, cyclophosphamide, vincristine, and dexamethasone

direct antiproliferative effect of the antibody, on complement-dependent cytotoxicity, or on antibody-dependent cell-mediated cytotoxicity involving monocytes, macrophages, lymphocytes, or granulocytes. They have also used antibodies coupled to a cytotoxic agent, such as radionuclides, toxins, or chemotherapeutic agents. In the case of the conjugated antibodies, their effectiveness does not rely on effector cells or the complement system but rather on the toxic properties of the conjugate. The use of radiolabeled antibodies was first reported in the early 1950s. Besides iodine 131, the isotope that Lam plans to use, bismuth 212, gallium 67, rhenium 186, and yttrium 90 have been used. While ^{131}I has been the most commonly used isotope because of its ease of conjugation and handling, the γ-rays it emits penetrate more than 10 cm in human tissue, thereby delivering radiation to more than just the tumor. Most of the trials of radiolabeled antibodies in lymphoma have targeted B-cell antigens. Only one trial reports the use of a radiolabeled anti-idiotype monoclonal antibody targeting the idiotype. A partial tumor regression was observed in the one patient who was treated.

The novelty in Lam's proposed approach lies in using peptides instead of antibodies to deliver the radiation. Lam correctly points out the advantages of peptides over antibodies, particularly the low molecular weight leading to improved tissue penetration, the ease of production and modification of peptides, and the lack of reticuloendothelial system uptake and immunogenicity. Whether analogues with higher affinity can be found remains to be seen, and a turnaround time from biopsy to treatment of two to three weeks is unrealistic, particularly considering the quality control that needs to be done before human administration.

The underlying hypothesis of the peptide ligand approach is that a linear peptide can mimic any structure. The ligands of immunoglobulins, however, can consist of proteins, carbohydrates, nucleic acids, or lipids. It remains to be seen if a peptide ligand can be found for every immunoglobulin tested. Lam intends to use an innovative technology, "selectide technology," which is a clever way of synthesizing millions of different peptides on solid-phase beads. One or several peptides that bind to the idiotype will be selected from a library of millions of peptides on beads. The hope is that among the random combinations of amino acids, one or several may have a high affinity for the target in question. The likelihood of finding a ligand increases with the number of peptides used for screening. With the selectide technology, 10^6 to 10^7 peptides can be screened. With phage display libraries, 10^8 to 10^9 peptides can be screened.[13] The advantage of the selectide technology over other combinatorial libraries remains to be shown. In a recent study, Barrett and co-workers used filamentous phage libraries displaying random hexapeptides to screen a monoclonal anti-β-endorphin antibody.[14] They identified phage bearing the original pentapeptide that the antibody was created against, as well as other ligands with nanomolar affinities, a result comparable to that reported by Lam.

Other obstacles in any approach targeting the idiotype are the selection of tumor clones expressing variants of the idiotype or no immunoglobulins at all. Perhaps variant cells will be eliminated by their proximity to cells expressing the idiotype that will be coated with the radioactive peptides. Overall, we are optimistic that the course Lam maps out will be successful. The experience gained by his research may lead to developments in targeting other receptors to treat cancers or autoimmune disease. We see a whole new field of peptide technology emerging. Current techniques allow the synthesis of millions to billions of randomly arranged nucleic acids or amino acids from which biologically active molecules with high specificity can be selected, much like nature selects from cells carrying random genes those that produce an antibody with high specificity.

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Ileus and Ignorance

WITH THE INTRODUCTION OF general anesthesia, antisepsis, and later asepsis, the success of the treatment of intra-abdominal disease by operation increased dramatically. This remarkable achievement was tempered by the recognition that mechanical manipulation of the bowel was accompanied by a temporary paresis of bowel activity that typically lasted from five to seven days. Early in this century, bowel dysfunction after an operation was life-threatening as oral intake was accompanied for several days by intractable vomiting, distention, aspiration, cardiac arrhythmia, and even death from "acute gastric dilatation." In the absence of sterile solutions for intravenous replacement, surgeons resorted to cumbersome infusions into the rectum and subcutaneous tissues ("clysis") to avoid profound dehydration. This digestive derangement was called "paralytic" or "adynamic" ileus to emphasize its transitory and functional nature and to distinguish it from time-honored mechanical ileus or dynamic intestinal obstruction. Despite countless explanations and remedies proposed over the past 100 years, the problem of postoperative ileus remains largely unresolved. Now, in this issue of the journal, Disbrow and co-workers propose the bold new idea that carefully directed preoperative suggestion has the power to hasten the return of bowel function after an operation.[1]

Aboral propulsion of liquid, gas, and chyme is the result of highly integrated activity of the stomach, small intestine, and colon. Parasympathetic nerves stimulate bowel contraction and relax enteric sphincters, thereby facilitating propulsion, whereas sympathetic nerve stimulation inhibits bowel activity and promotes ileus. Because many of the signs and symptoms of postoperative ileus—meteorism, hypoactive bowel sounds, anorexia, vomiting, and lack of flatus with exacerbation by eating and drinking—resemble those seen with acute nonabdominal conditions such as meningitis, pneumonia, and fractures, primary causation has long been attributed to "stress" or sympathetic-catecholamine overactivity.

A major step in understanding the pathogenesis of ileus was made when Wangensteen showed by careful studies in animals and patients that the bulk of intestinal gas arises from the swallowing of air and that symptomatic relief of acute ileus can be achieved by inserting a flexible tube into the stomach, causing immediate gastric decompression.[2] The recovery of bowel activity is spontaneous but variable, with the small intestine evincing segmental contractions even during an operation and coordinated peristalsis restored four to six hours after wound closure. In contrast, gastric paresis typically lasts two to three days, right colon inertia three to four days, and dysfunction of the entire colon as long as five to six days before gas traverses the full length of the digestive tract. With the recognition that cardiac rhythm is regulated by myoelectric wave conductance through the sinoatrial and atrioventricular nodes to the ventricular chambers, an analogous concept gradually evolved to invoke an intrinsic gastrointestinal pacemaker for the control of peristalsis.[3]

Based on these limited insights, many innovative therapies have been advocated to accelerate the return of peristalsis after a laparotomy. Parasympathomimetics such as bethanechol chloride and neostigmine (an anticholinesterase), ganglionic blockers such as guanethidine, smooth muscle stimulants such as pilocarpine, cholecystokinin, motilin, and ceruletide (caerulein), α-adrenergic antagonists such as chlorpromazine and phentolamine, β-adrenergic blockers such as propranolol, dopamine antagonists such as metoclopramide, and vasomediators such as vasopressin, prostaglandins, and dihydroergotamine were each introduced and championed for decades but eventually found wanting. Other remedies have included the administration of supplemental oxygen and even pressurized (hyperbaric) oxygen to wash out slowly diffusible intraluminal nitrogen, spinal anesthesia to block preganglionic sympathetics, pantothenic acid (a necessary substrate for coenzyme A and the synthesis of acetylcholine), hypertonic saline solution, whole blood transfusions, hot packs on the abdomen, and even operations such as adrenalectomy, ileocolectomy, or multiple "blow-hole" enterostomies. Again, after initial enthusiasm, these "panaceas" were eventually abandoned. The insertion of pacing electrodes for the direct stimulation of bowel contraction has also had disappointing results, as has transabdominal cutaneous nerve stimulation, a technique more akin to acupuncture than to western physiologic science. The discovery of enkephalins (opiate receptors) in the intrinsic nerve plexus of the bowel wall has encouraged the administration of antinarcotics such as naloxone to treat postoperative ileus.[4] Whereas the (ab)use of morphine, heroin, and other natural and synthetic narcotics is often responsible for severe constipation and obstipation, the use of opiate antagonists for the treatment of adynamic ileus remains unconvincing. Some data support the efficacy of an indwelling nasogastric balloon tube with "suction busting holes" to evacuate all swallowed air and thereby relieve bowel distention; a standard nasogastric tube is notoriously inefficient for this purpose and actually aggravates the swallowing of air. Whereas this specially designed balloon tube permits early postoperative feeding, its routine use has not gained widespread acceptance for simple procedures such as appendectomy and cholecystectomy and is potentially risky for complex operations involving bowel resection and a fresh anastomosis, such as gastrectomy and colectomy. Despite studies documenting that postoperative ileus is largely independent of the duration of the operation or of anesthesia or the degree of bowel manipulation, minimally invasive operations such as lap-

aroscopic cholecystectomy or fallopian tubal ligation and simple appendectomy are rarely accompanied by impaired gastrointestinal function, and oral intake is generally well tolerated within 24 hours of the procedure.

In this setting of hypothetic neurogenic, metabolic, pharmacologic, and inflammatory mediators in the pathogenesis of postoperative ileus but with general ineffectiveness of available treatment, Disbrow and colleagues examine the concept that increasing patients' awareness of impending bowel dysfunction preoperatively might shorten its duration postoperatively.[1] In a carefully designed prospective protocol, they establish reasonable criteria to monitor the development of ileus and to compare the time of the return of bowel function in two demographically comparable patient groups. One subgroup (control) received standard verbal reassurance regarding the impending operation, and the other (experimental) received specific "instructions" regarding the upcoming bowel dysmotility and the desirability of oral intake as soon as possible after the operation.

At first blush, the efficacy of such psychological reinforcement seems counterintuitive because conventional wisdom teaches that autonomic function is involuntary and independent of conscious thought. Yet, as Disbrow and associates point out, several clinical and experimental studies support the notion that the digestive tract is receptive to "learning," either by direct brain stimulation as in rats or through skinnerian operant conditioning in patients with intractable vomiting, fecal incontinence, or esophageal motility disorder. Perhaps an even more telling example of the influence of thought processes on autonomic function is peptic ulcer disease. Although recent evidence implicates bacterium (*Helicobacter pylori*) in the genesis of stomach ulcers, almost 175 years ago Beaumont described hyperemia of the stomach and the outpouring of gastric juice when Alexis St Martin, a young man with a permanent gaping, prolapsed gastric fistula as a result of a shotgun wound, became angry and upset.[5] A modern version of near-identical gastroautonomic responses to anger and hostility was reported in the case of "Tom," a victim of childhood corrosive gastritis and a well-developed, herniated, redundant gastric stoma.[6] Recognizing the role of psychic factors in the development of gastric and duodenal ulcers, Dragstedt extended the observations of Pavlov and documented the hypersecretion of acid-rich gastric juice between meals—for instance, at night—in patients with an ulcer diathesis and then showed that the interruption of vagal nerve bundles promoted ulcer healing.[7] In fact, until the widespread use of histamine (H_2) and proton blockers, disconnection of the brain-autonomic axis—that is, transecting vagi—was a common way to treat intractable peptic ulcer. Other gastrointestinal disorders thought to be "consciously" mediated through the autonomic nervous system include spastic colitis and irritable bowel, disorders characterized by recurring vague abdominal pain and intermittent diarrhea in high-strung people. Long postulated, too, but far from proved is the emotional or psychosomatic component responsible for the disabling inflammatory bowel diseases of regional ileitis and ulcerative colitis.

Other information also supports the influence of the psyche on autonomic dysfunction, with the relief of signs and symptoms by suggestion through biofeedback. Thus, with repetitive training, hand temperature, sweating, blood pressure, and even heart rate can be consciously self-regulated, and such learned behavior is used effectively to treat migraine, hypertension, and certain atrial arrhythmias and even to subvert the results of a polygraph or lie-detector test, a device that primarily depends on the interpretation of autonomic reactions—breathing, blood pressure, and the galvanic skin response.

Using blinded observers for ranking intraoperative bowel manipulations and assessing recovery variables from postoperative ileus, including time to first passage of flatus and length of hospital stay, Disbrow and associates found that instructed subjects (experimental) had a statistically shorter duration of ileus and earlier discharge than noninstructed but nonetheless reassured patients (control). There were also trends showing that instructed patients had a more rapid return of bowel sounds, faster removal of the nasogastric tube, and an earlier oral intake of liquids, with projected savings in hospital costs and, of course, less patient discomfort overall. Even though the ranking of operative criteria was carefully defined, it still would have been preferable to know exactly what operative procedures were done in the two groups. Moreover, with only 20 patients in each subgroup, a crossover of marginal data in as few as one or two patients may have negated the trends and statistical significance of the trial. Finally, past experience with "conscious activation" and autonomic (dys)function, such as in the development of peptic ulcer or biofeedback control of migraines, indicates that considerable time must transpire or conscious effort be expended—in other words, far greater mental activity than that afforded by a briefing just before an impending laparotomy.

Despite these criticisms and some skepticism, support for this study comes from findings after subliminal suggestive stimuli in patients operated on under general anesthesia. In these asleep patients, in contradistinction to awake subjects, specific ideas are verbally transmitted under full anesthesia. Although explicit memory—that is, free recall, cued recall, recognition, or free association—shows no retention, implicit memory or information processing is preserved by the performance of specific tasks by the patients after the operation in response to therapeutic suggestions transmitted under anesthesia.[8] Indeed, Cork and co-workers conclude, "[I]f this technique [intraoperative suggestion] could be further developed, perhaps common postoperative side-effects (e.g., nausea, emesis, difficulties with bowel and bladder function) could be minimized and pain management and overall outcome could be improved."[9(p897)] Whereas it is still premature to conclude that loud and coarse hard-rock or rap music subliminally seduces listeners into committing violent crimes, it is not overly far-fetched to consider that after a century of groping

ignorance and therapeutic paralysis, postoperative ileus may someday yield to simply putting in a few well-timed good words just before, during, and after an operation.

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Correspondence

Reserpine and Thiazide for Hypertension—An Inexpensive Therapy for Older Patients

To the Editor: Mana Hobson, MD, is to be commended for an excellent review on medications in older patients in the November issue.[1] It covers an extremely important area of clinical medicine for practitioners caring for older patients.

I suggest an addition to Hobson's comments on antihypertensive drugs. She begins by pointing out the comparative safety of low-dose diuretics, followed by a discussion of the relatively frequent adverse reactions to the other commonly used antihypertensives. But she does not mention the fairly well-tolerated regimen of adding 0.125 mg of reserpine with a diuretic daily. The efficacy of the combination of a thiazide and reserpine is well established.[2]

Hobson properly points out the concern with noncompliance, which has been shown to be linked to issues of cost, the complexity of the regimen, and the nature of side effects of the various drugs.[3] These comments should once again bring to our attention the value of a drug regimen rarely recommended today but still of great value, namely the combination of a thiazide and reserpine.[2] As we have previously pointed out, reserpine is remarkably inexpensive (less than $1.50 per month), is effective on a once-a-day dosage,[4,5] and, when used in doses of 0.125 mg, has minimal adverse effects.[6]

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Assessing CME Needs Assessment

To the Editor: Over the past century, physicians have faced increasing pressures to keep up with burgeoning medical progress. Beginning in the 1970s our state of Washington and others enacted legislation to mandate such efforts. Many required attendance at formal courses. An accreditation mechanism was devised to classify such offerings, with the "gold standard" being termed a Category 1 offering. Over the ensuing generation, a new industry has emerged to enable an educational unit to comply with the rules and regulations of the accrediting authorities—one of which is demonstrating that a "needs assessment" was conducted before the continuing medical education (CME) program was developed. Many purveyors expend considerable effort in documenting that they have sought out the needs or wants of prospective attendees. While a few revert to seeking inferences from local quality assurance or improvement efforts, in our state confidentiality concerns may thwart such activities. Our current 18 purveyors all conduct their own CME consumer surveys and are disappointed with 10% to 20% returns.

To improve the percentage of returns—if not necessarily to make them more meaningful—and to reduce cost drastically, a proposal was made to our state's Board of Medical Examiners. Would it, at the time of the biennial relicensing effort, accompany the form with a simple needs assessment questionnaire and ask that it be returned with the licensure check?

The envelope-sized form asked the recipient—after noting that the effort had been endorsed by the state medical association, the University of Washington's CME program, and the programs of the other CME purveyors in our state—to answer six open-ended questions, with one focusing on the recipients' perceived needs for their individual CME. The forms were sent to the investigators for tallying, and the results were fed back to all the purveyors in the state for their possible use.

The pilot program was initiated in July 1991 and carried on for some six months; the initial batch of 1,740 completed forms was tallied in December 1991 and a second batch of 2,650 in March 1992. More than 60% of the relicensees submitted usable questionnaires. Both investigators extracted a random sample of 350 completed forms for actual tallying. From the second batch, we extracted two random samples of 200 each to assess the question of sample variation. Several inferences might be of value:

- Not a single criticism of the effort was detected on any of the forms themselves or in the interesting letters that accompanied a number of them. To the contrary, "It's about time someone did this!" was noted repeatedly.
- A wide diversity of needs and wants was apparent. Only one item appeared more than seven times among the final 400 forms, suggesting to us that responders thought they had a distinctively different set of educational objectives, implying that attending any Category 1 course or reading any journal or text was a compromise between what each person wanted and what was being provided.
- Although a few indicated that additional information about human immunodeficiency virus issues was desirable, that topic led the list of excessive offerings in the previous year.
- While only 1 of the final 400 respondents listed viewing videotapes as the most valuable learning mecha-

nisms, more than 25% saw that technique as the wave of the future.

• When weighted averages were computed, reading medical journals was overwhelmingly seen as the most common source of responders' continuing medical education—accounting for 42% of the total.

From our perspective, this project has proved highly productive. The needs assessment should satisfy the most hard-bitten of accreditors as they tend to view with alarm more modest efforts on the local scene. A number of heretofore noncommunicating parties began to look at a common problem just as cost containment was taking center stage. The wide diversity of interests among these physicians carries a clear message to any of us who would oversimplify the process of lifelong learning by striving to rigidify and regulate it. Libraries can teach us all a valuable lesson as they dedicate their efforts primarily to responding to their customers' wants—as customers define them. Librarians see what is popular—what people read or borrow—and respond accordingly. They tend not to pay too much attention to third parties who would dictate or censor their offerings. The message seems clear: keep CME responsive to the professional customer. Try to find out if your programs are better received after a formal needs assessment effort as opposed to a far less formal and inexpensive one—and see if there is a detectable difference. In the meantime, our results are available to one and all for the cost of a stamped, self-addressed envelope—in tribute to cost containment on the one hand and to skepticism of the educational establishment on the other.

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Otitis Externa and Facial Cellulitis From Oriental Ear Cleaners

To the Editor: Otitis externa can be caused by a number of foreign bodies that traumatize the ear canal. If untreated, the infection can lead to facial cellulitis. Oriental ear cleaners are commonly used in the Asian community. They are known as *mimi kaki* in Japanese and *kwi shi shi gee* in Korean. Their main function is to clean the ear of cerumen and relieve itching associated with ear irritation. They are usually made of a strip of bamboo with a carved-out spoon at one end. We describe two cases of otitis externa caused by using Oriental ear cleaners.

Within a four-week period, a 64-year-old man of Japanese descent and a 65-year-old Korean man were seen with similar complaints of left ear pain and swelling associated with left facial swelling, pain, and redness. Neither had had any face or ear trauma, but both had used Oriental "cotton swabs" three to four days before being seen by a physician. In both patients, findings of a physical examination were consistent with otitis externa and facial cellulitis. Both were treated with antibiotics with complete resolution of signs and symptoms.

The anatomic position, hairs, and cerumen of the external ear all aid in the process of protecting the body from pathogens entering. Removal of the cerumen or the habit of scratching the ear canal with any object can cause perforation of the protective epithelial layer, providing an entrance for organisms that can cause infection, with the possibility of cellulitis as a complication. In these patients, a break in the epithelium and the resulting infection of the ear were probably due to abrasion caused by the scratching effect using the irregular surface of the bamboo cup.

From an informal survey of retail stores, we estimate that 6,000 to 7,200 of the bamboo ear cleaners are sold in a year to the southern California Japanese community alone. Physicians should be aware of the widespread use of these ear cleaners and warn their patients of the possible sequelae.

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Future Directions in Sickle Cell Disease

To the Editor: The discussion by Stamatoyannopoulos of future strategies for the management of sickle cell disease made interesting and informative reading.[1] Research in several directions aimed at ameliorating the morbidity and mortality of this hemoglobinopathy has yielded promising results. While pharmacologic stimulation of hemoglobin (Hb) F synthesis, particularly with hydroxyurea, has been the most important advance in this regard, drugs with effects other than on Hb F synthesis have also been shown to be of value, not only in in vitro studies but also in human clinical trials. I would like to mention in brief the rationale for some of these agents.

When intracellular polymerization of Hb S occurs, the red cell membrane undergoes a number of secondary changes in proteins and lipids that can result in abnormal ion content, transport, and volume regulation. Cetiedil citrate, a membrane modifier, associates with the red cell membrane, inhibiting calcium-activated potassium efflux and increasing passive sodium influx.[2] This prevents cell dehydration and provides an antisickling effect. Benjamin and colleagues, in a double-blind placebo-controlled study in 67 patients presenting within 24 hours of crisis onset, demonstrated a significant ($P < .001$) reduction in duration of crisis compared with the use of placebo, with no important adverse effects.[3] Similarly, Teuscher and associates in 1989 reported the results of the first controlled study of intravenous pentoxifylline, a hemorheologic agent that increases red cell deforma-

bility and reduces viscosity and peripheral vascular resistance; they showed a shortened duration of crisis ($P < .03$) compared with placebo.[4]

A role for arteriolar vasospasm in the early stages of sickle vaso-occlusive events has been proposed; the effects of the vasodilator nifedipine on retinal and conjunctival vessels in patients with sickle cell disease was studied by Rodgers and co-workers.[5] Treated patients showed a reversal of sickling-induced retinal arteriolar occlusion and a reduction in the conjunctival "comma sign," considered to represent localized areas of segmentation due to vasoconstriction and to be pathognomonic of the sickle syndrome. Finally, an aldehyde called 12-C-79 has been shown to reduce Hb S polymerization in humans by directly increasing the solubility of Hb S; it is currently undergoing clinical evaluation.[6]

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Singapore's Solution to Health Care Costs

To the Editor: The American Medical Association has reported that over 40% of United States health care costs are directly attributable to American self-indulgence, coupled with our polyglot ethnic diversity and propensity to settle disputes with bullets. Tobacco, intravenous drug use, unsafe sex habits, excess alcohol and dietary fats, coupled with sedentary life-styles and lackadaisical driving habits, ratchet up health costs while Americans expect, nay even demand, that someone else pick up the tab.

Singapore has evolved a health insurance plan based on individual responsibility, not rights and privileges.[1] Article 5 of the policy statement of Mr Yeo Cheow Tong, the Singapore Minister of Health, reads:

"Our medical system is based on individual responsibility . . . no Singaporean has enjoyed or expects to enjoy health services for free. When hospitalized he pays part of the bill, more in a B class than in a C class ward. His Medisave is his *own money*. This gives him the incentive to be healthy, minimize his need for medical treatment, and save on medical expenses."[1]

The individual Singaporean savings account, established in 1984 as "Medisave," is a system the United States could well copy. Each person contributes to his or her own Medisave account—currently at 6% of income—to meet future medical expenses of the immediate family. Article 35 of the Medisave government policy reiterates and clearly defines the role of each citizen in terms of personal responsibility for health. "Every Singaporean has the duty to stay fit and healthy. A healthy life-style will reduce his chances of falling sick. He should save up for future medical needs by contributing regularly to Medisave. He should use his Medisave prudently, by choosing the class of ward which he can comfortably afford."

Adopting a Medisave system by US workers would dramatically increase the nation's saving rate, currently at an all-time low compared with competitors such as Japan and Germany. Invested savings provide the capital necessary for economic growth. Such a system would also establish in the minds of US citizens their own individual participation in, and accountability for, paying for their health care.

The problems of the Scandinavian, British, and Canadian health systems have shown that centralized government control and administration of health care are unsustainable. Eventually they all collapse in the face of unremitting and escalating demands for more and more "free" care while the countries' economies flounder under the weight and burden of taxes, stifling job growth and economic expansion.

Medicine costs more because we can do more. People live. People live longer. The people should have the final say in how each cent of their health care is bought and paid for. Our government can help by setting up tax-free medical savings accounts.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

First Day of Class

DANA F. HOCH, MD, *San Jose, California*

The 3 second-year medical students lingered just outside the hospital room, looking vaguely apprehensive and a little excited. It was the first day of their "Introduction to Clinical Medicine" course. The dispassionate world of the lecture hall and laboratory had been replaced by the mystery and real-life urgency of the hospital. Earlier that day each of the students had performed a history and physical examination on a patient. All three of the cases had been presented to me, and it was time to meet the first patient.

I led the way into the room, strode up to the second bed, and casually flipped through the vital signs clipboard. "I'm Doctor Hoch, Mrs Harris," I announced cheerily. I noticed the students hesitating just inside the door as they eyed me uneasily. "These students are learning about patients and sickness and the physical examination. You've met one of them, right?" With a wave of my hand I motioned them inside and hooked a finger at Cheryl, the student who had reported on Mrs Harris.

"Yes," Mrs Harris nodded from her bed. She wore an accommodating smile. Her face was heavily seamed and aged beyond her 40 years. She had a dreadful case of rheumatoid arthritis and the day before had been admitted with severe anemia and a gastrointestinal hemorrhage. Clear intravenous tubing, transformed to the dull red color of beets, hung from a bag of packed red cells.

"Mrs Harris, what was it like when you first developed your illness?" I asked.

"Well, Doctor, I've never been asked that question exactly." She paused a moment. "What I remember mostly was how I just thought my toes were sore from too much aerobics."

Mrs Harris then recounted how her life had been changed by the natural course of her disease. She consulted more than one physician because of her feet and shoulder pains, but the diagnosis was missed for months. Accustomed to regular exercise and a life of physical fitness, she struggled at first to maintain her routine. "I just wanted the doctors to help me continue my exercising and to have a normal life with my kids." Ultimately she faced the realities of gold injections, tendon implants, and a new routine: life with a chronic illness.

"Of course, I can't do aerobics anymore, but I have been able to take care of my kids still." She fell silent and her eyes spoke volumes. She brushed back tangled brown hair from her face and, in the easy manner of experienced patients, displayed her body for the physicians. We examined her twisted skeleton and the joint deformities; the students looked with gaping, almost fearful interest, as if Mrs Harris's limbs were about to snap.

As we left the room, Mrs Harris called out, "Thank you, doctors, thanks a lot." We waved to her on the way out and moved on to the other two patients.

Later we gathered at the nurses' station. The students spoke excitedly of their patients and the physical findings: a gallop rhythm of heart failure, ascites, and hepatomegaly. This was pathophysiology come alive after two years of inanimate preclinical studies.

"What was the most amazing thing you learned today?" I asked.

"I heard a third heart sound!" Cheryl beamed.

"That is important, sure. But why do you think Mrs Harris thanked us? After all, we only took her history and some of her time, yet she gave us so much more." They exchanged puzzled looks.

"We validated her life and her suffering, we gave it meaning," I said. She had been accustomed to physicians scrutinizing her disease from the artificial shelter of medical science, where the rheumatoid arthritis was of most interest. "Instead, we were interested in what is for her far more important than science and diagnosis, the subjective world of her suffering. Ironically, by so doing we helped her survive another day."

I looked carefully at the faces of the students. They seemed vaguely interested. They had heard this sort of thing before and knew what I said was relevant, but it certainly was not information required to pass the course.

"If you listen closely, patients will not only tell you how they endure but teach lessons that may help you endure. Now that is a splendid gift, isn't it? And it happens every day of your career."

I left them at the nurses' station, with the hope that I had taught them something useful about taking a history and doing a physical examination. But I knew that whatever I had taught them was insignificant compared to what Mrs Harris had done for them.

(Hoch DF: First day of class. West J Med 1993 May; 158:538)

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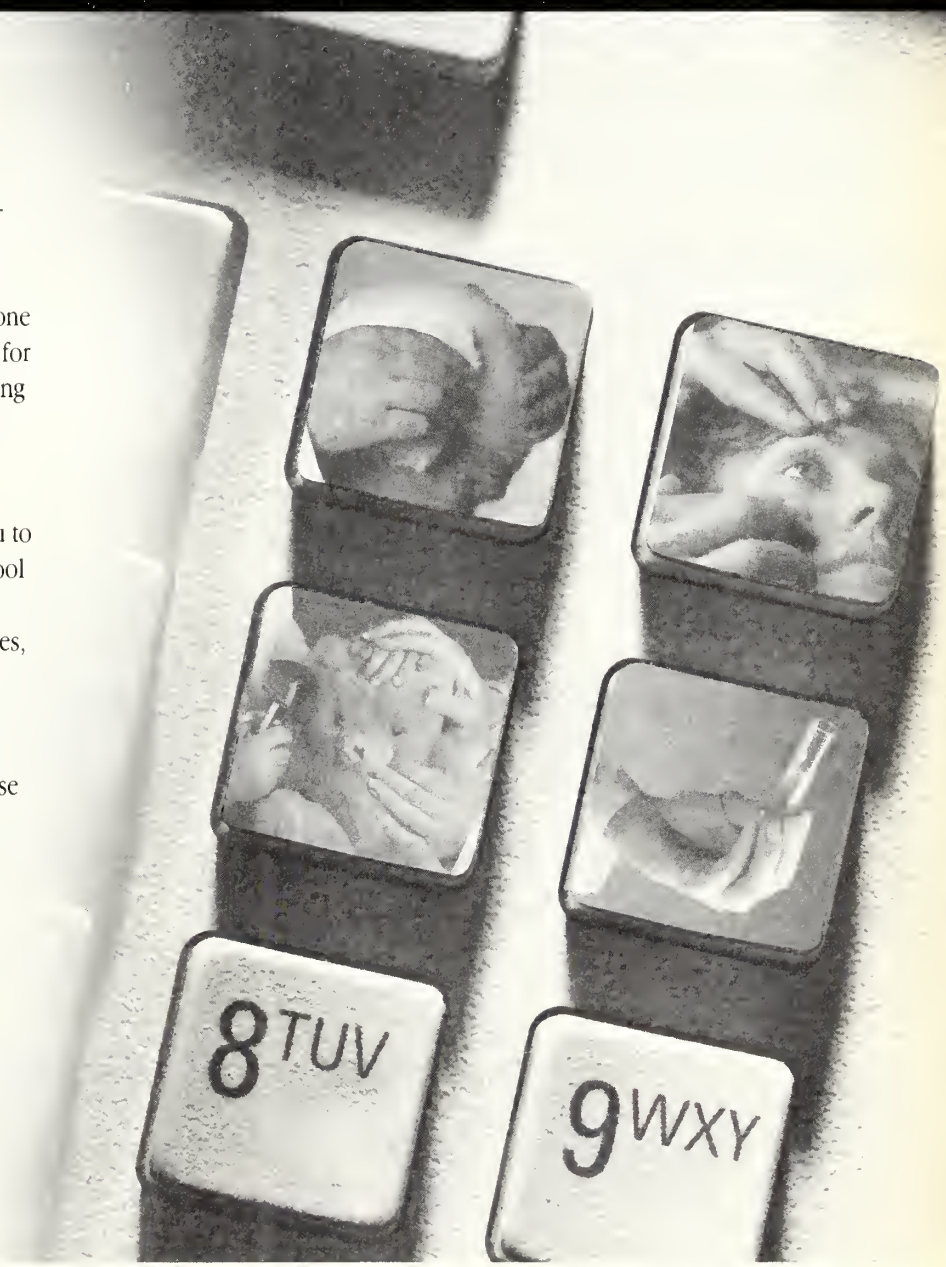

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- Kenneth Norris Jr. Cancer Hospital & Research Institute
- USC University Hospital

(Continued from Page 473)

GENERAL/MULTIDISCIPLINARY

June 11-13—**The Medical Office Laboratory Conference.** SDSU at San Diego Red Lion Hotel. Fri-Sun. 20 hrs. $425. Contact: Nancy Geiser, (619) 594-6255.

June 25—**Bioethics Conference.** UCD at Hyatt Regency, Sacramento. Fri. Contact: UCD.

October 14-17—**Women in Medicine.** UCSD at San Diego Hilton. Thurs-Sun. 15 hrs. $300. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Advances in Clinical Rheumatology and Update in Clinical Rheumatology Home Study Courses. Cleveland Clinic Foundation. 26.75 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, New Jersey 08034-1457. (800) 284-8433.

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

CME Home Study Program Modules. UCSD.

Urology Video Program. UCLA. 24 hrs. Contact: CME Video, 1916 Old Cuthbert Rd, B-13, Cherry Hill, NJ 08034-1457. (800) 284-8433.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 10-11—**Basic/Advanced Fetal Monitoring Program.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Trish Beachy, (303) 270-8376.

June 10-11—**Neonatal Resuscitation Program Provider Course.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Fri. Contact: Outreach Office, (303) 861-6668.

June 10-12—**Sixth Annual Summer in the Mountains Conference.** Children's Hospital at Battlement Mesa Conference Center, Parachute. Thurs-Sat. Contact: Mary Haley, (303) 270-8376.

June 14-16—**Community Health Traineeship Program.** Children's Hospital, Denver. Mon-Wed. Contact: Outreach Office, (303) 861-6668.

July 13—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

July 30-August 1—**Second Annual Medical Ethics Conference.** University of Colorado Health Sciences Center at Aspen. Fri-Sun. Contact: Phyllis Schroeder, U of Colo.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

August 23-27—**18th Annual Musculoskeletal Care.** University of Colorado Health Sciences Center at Breckenridge. Mon-Fri. Contact: Phyllis Schroeder, U of Colo.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

CONTACT INFORMATION

U of Colo—Contact University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

IDAHO

July 28-31—**Imaging on Lake Coeur d'Alene—A Summer Radiology Meeting on One of the Five Most Beautiful Lakes in the World!** Coeur d'Alene Resort, Coeur d'Alene. Wed-Sat. Contact: Kathy Fischer, Sacred Heart Medical Center, Department of Radiology, PO Box 2555, Spokane, WA 99220-2555. (509) 455-3352.

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

NEW MEXICO

Information, requests for accreditation, and items to be listed should be sent to the chair of the CME Committee, New Mexico Medical Society, 7770 Jefferson, Suite 400, Albuquerque, NM 87109, at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 828-0237.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 15—**New Mexico Physicians Mutual Liability Company Loss Control Seminar.** Holiday Inn Pyramid, Albuquerque. Sat. Contact: Sue Wunderlin, NMPMLC, 7770 Jefferson NE, Suite 410, Albuquerque 87109. (505) 821-9485 or (800) 880-9485.

September 10-11—**New Mexico Chapter, American College of Surgeons Annual Meeting.** Holiday Inn Pyramid, Albuquerque. Fri-Sat. Contact: Bonnie Smith, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 269-5883 or (505) 828-0237.

October 1-2—**John N. Wilson, MD, Lectureship in Cardiology: Cardiology '93.** Albuquerque Hilton Hotel. Fri-Sat. Contact: Mary Boning, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

October 16—**New Mexico Orthopaedic Association Annual Meeting: Sports Medicine.** Inn at Loretto, Santa Fe. Sat. Contact: Elsa Hall, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 828-0237.

CONTACT INFORMATION

UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. Accredited institutions wishing to list AMA Category 1 CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, UT 84102; or phone (801) 355-5290. For information on CME accreditation, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution.

(Continued on Page 542)

SOUTHERN MEDICAL ASSOCIATION

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

JUNE 4-6, 1993

THIRD ANNUAL FOCUS ON PEDIATRIC AND ADOLESCENT PATIENTS
LOCATION: Sandestin Resort and Conference Center, Destin, Florida
SPECIALTY: Primary Care, Pediatrics
CME CREDIT: CAT I-13; AAFP 12.5 Prescribed; AOA 12.5 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$195

JUNE 11-13, 1993

PHYSICAL MEDICINE AND REHAB UPDATE
LOCATION: The Ritz-Carlton, Naples, Florida
SPECIALTY: Orthopaedics, PM and R, Family Practice
CME CREDIT: CAT I-15; AAFP 15 Prescribed; AOA 15 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$195

JUNE 13-17, 1993

17TH SYMPOSIUM ON LUNG DISEASE
LOCATION: The Cloister, Sea Island, Georgia
SPECIALTY: Pulmonary Medicine, Critical Care Medicine, Internal Medicine
CME CREDIT: CAT I-24
FEE: SMA Member-$395; Nonmember-$520; Nonphysician-$200

JULY 9-11, 1993

THIRD ANNUAL OFFICE MANAGEMENT OF INFECTIOUS DISEASES
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Gynecology, Pediatrics
CME CREDIT: CAT I-15; AAFP 15.25 Prescribed; ACOG 15 Cognates; AOA 15.5 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 19-22, 1993

SECOND ANNUAL SURGERY UPDATE
LOCATION: The Cloister, Sea Island, Georgia
SPECIALTY: General Surgery
CME CREDIT: CAT I-14
FEE: SMA Member-$400; Nonmember-$525; Nonphysician-$250

JULY 26-29, 1993

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Obstetrics and Gynecology, Primary Care
CME CREDIT: CAT I-18; AAFP 18 Prescribed; ACOG 19 Cognates; AOA 18 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 30-AUGUST 1, 1993

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Urology
CME CREDIT: CAT I-14; AAFP 13 Prescribed; AOA 14 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

AUGUST 27-29, 1993

FAMILY MEDICINE UPDATE
LOCATION: Calloway Gardens, Pine Mountain, Georgia
SPECIALTY: Primary Care, Family Practice
CME CREDIT: CAT I-14, AAFP 14 Prescribed; AOA 14 CAT 2A
FEE: To be announced

For more information, call Michelle Williamson, Southern Medical Association, 800-423-4992 or 205-945-1840—TODAY!

CONTINUING MEDICAL EDUCATION

(Continued from Page 540)

July 5-9—**Update in Internal Medicine.** UUSM at Olympia Hotel and Conference Center, Park City. Mon-Fri. Contact: UUSM.

July 29-31—**Summer Shakespearean Meeting.** Cedar City. Thurs-Sat. Contact: UOS.

September 22-25—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

SPONSORS OF COURSES—ABBREVIATIONS

CH:	Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price 84501. (801) 637-4800.
CS:	Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM:	Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
FHP:	FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS:	Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH:	LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH:	Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
OSS:	Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC:	Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH:	Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA:	Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS:	Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH:	Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM:	University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
UV:	Utah Valley Regional Medical Center, 1034 N 500 West, Provo 84604. (801) 373-7850.
VAMC:	Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 15—**Infectious Diseases.** Seattle. Sat. Contact: U/W.

May 17-18—**Introduction to AIDS Clinical Skills for Primary Care Providers.** Seattle. Mon-Tues. Contact: U/W, (206) 720-4250.

May 20—**RX of Glomerulonephritis.** Bellingham. Thurs. Contact: (206) 676-1712.

May 22—**Pain Management for Primary Care Physicians.** Seattle. Sat. Contact: U/W.

May 27—**Pesticide Medicine.** Seattle. Thurs. Contact: Northwest Center for Occupational Health and Safety. (206) 543-1069.

(Continued on Page 543)

7th Annual

LOW BACK PAIN CONFERENCE

June 4-6, 1993

BALLY'S CASINO RESORT, LAS VEGAS

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Credit: University Medical Center, Southern Nevada designates this continuing medical education activity for 12.0 credit hours in Category I of the Physicians Recognition Award of the American Medical Association.

Registration: The registration fee for this meeting is $185. To register or receive more information, please call c/o Stanley Schultz, Inc., (800) 528-9906.

When: June 4-6, 1993. Lectures begin at 6:30 PM on the 4th and conclude at noon on the 6th.

Where: Bally's Casino Resort, Las Vegas. Room rate is $75.00 single or double. To reserve a room, call 800-833-3308. One night's deposit required. After May 10, 1993, rooms subject to availability.

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The San Francisco
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(June 4)

June 4, 1993
Chemical Dependence in
Health Professionals &
Prescription Drug Issues:
National & State Perspectives

June 5, 1993
Medications Development in Addiction Medicine:
Clinical & Conceptual Issues

June 6, 1993
Medication,
Spirituality & Recovery

Call (800) 432-5585 for registration information

CONTINUING MEDICAL EDUCATION

(Continued from Page 542)

June 3-4—**Travel Medicine.** Seattle. Fri-Sat. Contact: U/W.

June 4-5—**Surviving the Elements.** Seattle. Thurs-Fri. Contact: U/W.

June 19—**Medical Malpractice: Biennial Update.** Seattle. Sat. Contact: U/W.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare. (206) 592-1221.

June 25-26—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

July 9—**Update From the IXth International AIDS Conference in Berlin, Germany.** Seattle. Fri. Contact: U/W.

August 2-7—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

August 27-28—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital, (206) 526-2501.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 13-17—**21st Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

October 8-9—**Society for Pediatric Pathology.** Seattle. Wed-Fri. Contact: Children's, (206) 526-2501.

October 22-23—**Adolescent Medicine.** Seattle. Thurs-Fri. Contact: Children's Hospital, (206) 526-2501.

October 27—**Perinatology Conference.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

November 18-19—**Regional Musculoskeletal Conference.** Seattle. Thurs-Fri. Contact: U/W.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEII, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WYOMING

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ♦

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BC/BE GASTROENTEROLOGIST NEEDED. Busy office practice. 27 doctor multispecialty clinic. Mountain locale. Guaranteed salary. Excellent benefits. CV to Mike McCraley, Ogden Clinic, 4650 Harrison, Ogden, UT 84403; (800) 234-5637.

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CALIFORNIA, PACIFIC NORTHWEST, ARIZONA. Positions in Family Practice, Internal Medicine, Orthopedics, Pediatrics and OB/GYN. Call or send confidential CV to Mitchell & Associates, Inc, PO Box 1804 Scottsdale, AZ 85252; (602) 990-8080.

(Continued on Page 545)

(Continued from Page 544)

PHYSICIANS WANTED

CALIFORNIA

Primary Care Physicians and Radiologists needed to work as locum tenens statewide. High salary, paid malpractice. Work whenever and wherever you wish. Permanent placements as well. **INTERIM Physicians/Western Physicians Registry; Northern California, contact Jim Ellis, (800) 437-7676. Southern California, contact Tracy Zweig, (800) 635-3175.**

GERIATRICIAN AND GENERAL INTERNIST POSITIONS, Assistant/Associate Clinical Professors (San Diego, California). The Department of Medicine, Division of General Internal Medicine at the University of California, San Diego is seeking two BC General Internists and a BC Internist or Family Physician with training and experience in Geriatric Medicine. Each position is 80% clinical to provide primary and/or specialty care to patients enrolled in managed care programs and 20% teaching. For the Geriatrician candidates, preference will be given to those with fellowship training and/or the Certificate of Added Qualifications in Geriatrics. Salary and benefits are competitive. Salary and rank commensurate with candidate's experience and based on established UCSD salary scales. Reply to Joe Ramsdell, MD, UCSD Medical Center, Dept of Medicine (8415), 200 W Arbor Dr, San Diego, CA 92103-8415; (619) 543-6275. Closing date is July 1, 1993; CVs received after this date will be considered until all positions are filled. AA/EOE.

INTERNIST TO JOIN busy three physician Internal Medicine group. Ideal time to establish a practice in paradise. Send CV to 901 Pacific St, Monterey, CA 93940; (408) 373-3153.

SAN JOSE, CALIFORNIA. An excellent opportunity for BC/BE OB/GYN to join four person OB/GYN department of large, established multispecialty group. Group is located next to 400-bed state-of-the-art hospital with LDR rooms and Level III Nursery. Exceptional salary and benefits package. Call coverage is 1.5. Call Florence Korbus collect at (408) 999-7113 or send CV to MMS, 532 Race St, San Jose, CA 95126.

URGENT CARE. WASHINGTON STATE. Urgent Care Center within 30 physician group seeks physician desiring practice with reasonable hours and workload. Located in the foothills of the Blue Mountains with nationally recognized liberal arts college, superb community symphony, excellent public schools, and plentiful recreational opportunities, including skiing, nearby. Guaranteed salary with incentive, excellent benefits, and retirement plans. CV to Administrator, Walla Walla Clinic, 55 W Tietan, Walla Walla, WA 99362.

IN ALBUQUERQUE, NEW MEXICO you will discover an abundance of sunshine, breathtaking scenery, and diverse recreational and cultural pursuits! FHP, one of America's most progressive HMOs, offers you the opportunity to explore the "Land of Enchantment's" many wonders while practicing in a setting that combines a balanced lifestyle with plenty of clinical challenge. All this and a guaranteed salary and benefit package, too! We are looking for a few good BC/BE Internal Medicine physicians to join our exceptional 24 provider group. Contact Mary Consie, (800) 444-4347, or write FHP, 4300 San Mateo NE, Albuquerque, NM 87110. EOE.

PHYSICIANS. We operate six Community Health Centers in central California. We have an opening for a Family Practitioner and an Internist to join our Pediatrician and Physician's Assistant at our new modern clinic in Wofford Heights. Located one hour east of Bakersfield in a beautiful mountain lakeside resort area. Full lab and x-ray services. Excellent salary and benefit package. Malpractice paid. Loan repayment available through NHSC. This is a rare opportunity to combine a very attractive lifestyle and an excellent practice opportunity. Call George Johnston at (805) 845-3731 for details.

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Internal Medicine & Family Practice

As one of the most successful HMOs in the Southwest, we have two very good reasons why you should join us at FHP Health Care® in Arizona. The first is your professional life. The second is your personal life.

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Call **1-800-535-4FHP** for additional information on FHP and Arizona. Or if you prefer, send your CV to: FHP Professional Staffing, P.O. Box 52078, Phoenix, AZ 85072-2078.

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PHYSICIANS WANTED

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Call (800) 727-2478 or FAX your CV in complete confidence to (408) 727-7390. Never a fee to the physician. **Nugent & Grant, 1400 Coleman Ave, Ste B24, Santa Clara, CA 95050.**

NATIONWIDE TRAVEL. Health research organization seeks physician for National Health and Nutrition Examination Survey sponsored by the US Public Health Service. Individual will be part of a large medical team conducting health examinations in government mobile exam centers traveling to 88 areas of the US through Fall of 1994. Must be licensed in one state. One year minimum commitment and full-time continuous travel required. Competitive salary, paid malpractice, per diem, car, four weeks paid vacation per year, holidays, and health, life, dental, disability insurance offered. Call Beverly Geline, (800) 937-8281, ext 8248. Westat, Inc, Rockville, MD. EOE/M/F/V/H.

BC/BE FAMILY PRACTITIONER with commitment to caring for the underserved, needed to join one Family Practitioner, Family Nurse Practitioner, one Pediatric Nurse Practitioner, and one OB/GYN Nurse Practitioner in Walla Walla, Washington. Shared call with two local OB/GYNs and four Family Physicians. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

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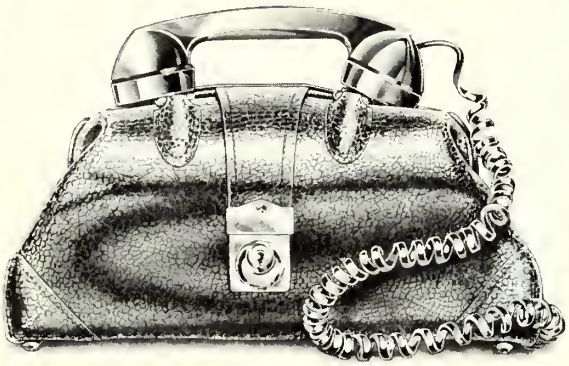

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(Continued from Page 545)

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Northwest Permanente, P.C., has an excellent opportunity for a Board Certified or Eligible Family Physician to join Kaiser Permanente's 50-physician multi-specialty group in Salem, a mid-sized city located in the lush Willamette Valley close to ocean beaches and mountains. The group provides a full range of professional services to 38,000 plan members in the area.

We offer a professionally stimulating environment, and a competitive salary/ benefits package which includes professional liability coverage, family medical/dental insurance, two pension programs, sabbatical leave, etc. For more information, send inquiry and C.V. to W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Suite 300, Portland, OR 97210-5398. EOE.

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CALIFORNIA. IME, QME, AMEs, Orthopedists, and Neurologists for established office in central/northern California. Excellent terms, flexible hours. Medical Specialists of California; (800) 606-9800.

FAMILY PRACTICE–REDONDO BEACH, CALIFORNIA. Nine physicians all BC; fee-for-service; 300 new patients per month; no HMO. Need residency trained Family Practitioner for summer 1993. CV to Lee Kissel, MD, 520 N Prospect, #100, Redondo Beach, CA 90277.

NORTHERN CALIFORNIA. Opportunities available with Comprehensive Medical Evaluations in Sacramento, San Jose, and Monterey bay area for BC physicians in Orthopedic Surgery, Psychiatry, Internal Medicine, and subspecialties, Dermatology, Neurology, Physical Medicine/Rehabilitation, Ophthalmology,Otolaryngology, Plastic/Reconstructive Surgery and Toxicology/ Occupational Medicine, to perform forensic medical evaluations. This is an excellent opportunity to supplement income without increasing your practice overhead. Send inquiry to Terence Doyle, Comprehensive Medical Evaluations, 87 Scripps Dr, Ste 308, Sacramento, CA 95825; or call (916) 567-3411.

OREGON. BC/BE GENERAL INTERNIST to join 21 member Internal Medicine department of 66 physician multispecialty clinic. University town. Guaranteed salary, incentive bonus, excellent benefits. Send CV to Richard M. Rytting, MD, Medical Director, The Corvallis Clinic, PC, 3680 NW Samaritan Dr, Corvallis, OR 97330.

(Continued on Page 547)

(Continued from Page 546)

PHYSICIANS WANTED

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NORTHERN CALIFORNIA

Several positions available for Internal Medicine, most medical subspecialties, ENT, Orthopedics, Anesthesiology, and OB/GYN. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

OPPORTUNITY–URGENT CARE AND FAMILY PRACTICE. Work, live, and play within minutes of any outdoor activities you ever dreamed of. Boise offers it all including culture and an excellent atmosphere for family living. Choose 12 or 24 hour shifts. Be able to have three and four days off in a row. No on-call duties. Work at one, two, or each of our multiple facilities covering Emergency Rooms and Walk-in Family Practice. Contact Janet Meyers at (208) 323-1223 or write 2153 Century Wy, Boise, ID 83709 to learn more about our new, exciting benefit package. (Positions also available in New Mexico.)

LUSH HAWAII, CALIFORNIA, AND TEXAS COAST clinics need Family Practitioners or Internists, to $110,000. Benefits/fee paid. OB/GYN, $130,000-$200,000. Share call. Invasive Cardiologist to $200k. CV to LAM Physician Associates, Dept W, 444 Hobron Ln, #207H, Honolulu, HI 96815-1229; Pat Lam; (808) 947-9815; toll-free (800) 258-4526.

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The California Department of Corrections has a number of opportunities available in the following areas:

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PHYSICIANS

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Or send CV to: John Zil, M.D., J.D., Chief Psychiatrist,
California Department of Corrections
Dept. DHCS, P.O. Box 942883, Sacramento, CA 94283-0001.
Fax **(916) 322-5864** EOE.

PHYSICIANS WANTED

FAMILY PHYSICIAN–LEWISTON, IDAHO

Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson; or call (208) 743-8416.

LAUGHLIN, NEVADA. The Laughlin Medical Center is offering an excellent opportunity for a Family Practice or Emergency Physician who would like to relocate to the fastest growing city in the western United States. We offer flexible hours, generous benefits, salary over $125K with incentive plan. Send CV to S. Schlotter, 2061 E Sahara Ave, Las Vegas, NV 89104; (702) 731-1278.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

SAN FRANCISCO EAST BAY. Primary Care group practice seeks associate for future partnership. Excellent patient mix, modern office near hospital. Collegial medical staff with support from 200-bed community hospital. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

SAN JOSE group and partnership opportunities in Internal Medicine, Family Practice, Pediatrics, and OB/GYN. This busy practice is affiliated with a 200-bed community hospital. For a detailed discussion and description of the practice offered in your specialty, contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

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Address inquiries to **Richard A. Lockwood, MD, Assistant Dean/Director of Medical Affairs, 445 S Cedar, Fresno, CA 93702.** Equal opportunity employer; women and minorities are encouraged to apply.

(Continued on Page 548)

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PHYSICIANS WANTED

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MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524

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Highly respected, 35 member multispecialty group seeks second Medical Oncologist to join a busy, regional practice. Group is site for CCOP protocols and practices out of one of Oregon's premier hospitals, which is seeking a quarter-time Medical Director for its cancer programs. Portland offers an outstanding quality of life near mountains and the ocean with diverse cultural and educational opportunities. Housing is affordable and schools are excellent! Compensation negotiable depending upon experience. **Call Pat Wall at (800) 462-1857 for more information.**

SEATTLE/TACOMA. Expanding multispecialty group practice seeks Family Practitioners and Internists. Excellent remuneration package with partnership after two years. Call every sixth night plus weekend. Great location, affordable homes, outdoors dream. Contact Ken Baker, Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

HAWAII. FAMILY PRACTITIONER WITH OB SKILLS and Internal Medicine physician needed for rural underserved area. Full-time position in nonprofit community health clinic. Desire dedicated person to work in multicultural setting. Contact Puanani Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Hwy, Waianae, HI 96792. (808) 696-7081.

ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

OPPORTUNITY. BC physician (Family Practice, Internal Medicine, or Occupational Medicine) for a busy private/industrial medicine practice in Los Angeles. Bilingual preferred (medical Spanish required). Clinic is affiliated with a major medical center. Excellent salary. Send CV to Number 281, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

SALT LAKE CITY–URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

INTERNAL MEDICINE/PRIMARY CARE. BC/BE, recently trained (university program preferred) for group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

NEVADA–GASTROENTEROLOGIST. BC/BE needed to join Gastroenterology practice in southern Nevada. Generous salary leading to full partnership. Send CV to K. Hicks, 6151 Mountain Vista, #525, Henderson, NV 89014.

CALIFORNIA. NONINVASIVE CARDIOLOGIST needed to join an invasive established Cardiologist. 8:00-5:00 office practice only. Short drive from San Diego and Los Angeles. Competitive salary and benefits. Send CV or call Anil Rastogi, MD, 2390 E Florida Ave, Hemet, CA 92544; (909) 652-5555.

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PRIMARY CARE IN THE PACIFIC NORTHWEST. Diverse opportunities for Family Physicians in urban and rural health centers throughout Washington, Oregon, Idaho, and Alaska. Loan repayment possible. Practice where it's nearly perfect. Send CV to Sarena Seifer, MD, Northwest Regional Primary Care Association, 4154 California Ave, SW, #7, Seattle, WA 98116; (206) 932-2133.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved, needed to join clinics in Milton-Freewater, and Hermiston, Oregon. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Jeri Weeks, Recruiting Specialist, at (509) 865-5898, or Sylvia Arroyo, Clinic Administrator, (509) 525-6650.

INTERNIST–INPATIENT SERVICE, COASTAL SOUTHERN CALIFORNIA. FHP Health Care, a leading HMO for over 30 years, currently seeks a BC/BE General Internist with superior inpatient skills to join the six-member Internal Medicine service in our beautiful 250-bed hospital in Orange County. Responsible for rounds, admissions, consults, cross-coverage, ICU/procedures, 23-hour observation unit. Daytime hours. Nine consecutive days off each month. Excellent salaries and benefits including outstanding retirement program, time off for CME, paid vacations, and much more. Send CV to FHP Health Care, Professional Staffing, Dept 45, 9900 Talbert Ave, Fountain Valley, CA 92708. EOE.

FLORIDA GULF COAST. Two BC Hematologists/Oncologists seeking third to join pure subspecialty practice. Competitive salary and excellent benefits. ECOG, GOG. Sophisticated medical community with a tropical climate. Send CV with cover letter to Practice Manager, 306 South Blvd, Ste B, Tampa, FL 33606.

THERE'S GREEN IN YOUR FUTURE. Thomas-Davis Medical Centers, Arizona's largest and most successful multispecialty group, needs an experienced BC/BE Internist or Med/Ped to join two others at its clinic in beautiful Green Valley, Arizona. Green Valley is located only 26 miles south of metropolitan Tucson. The retirement community of Green Valley offers picturesque views, suburban lifestyle, five golf courses, and shopping in Mexico. Top benefits, profit sharing, guarantee first two years plus incentive pay, early shareholder, and signing bonus. Call or write Dee Pones, (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732. FAX (602) 322-2676.

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PHYSICIANS WANTED

INTERNAL MEDICINE

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NORTHWEST PERMANENTE, P.C., has two excellent opportunities for Board Certified or Eligible General Internists to join our 16-physician primary care group in Longview-Kelso, Washington, a picturesque, stable community of 42,000 people. A full range of professional services are provided to Kaiser Permanente's 26,000 plan members in the area.

We offer a competitive salary and benefit package which includes two comprehensive pension plans, paid professional liability and sabbatical leave. **Forward C.V. and inquiry to: W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Ste. 300, Portland, OR 97210-5398. EOE.**

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Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty member. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a paramedic base station and training center, and in addition, has an active helicopter service and regional poison center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after July 1, 1993. The University of California is an Affirmative Action/Equal Opportunity Employer.

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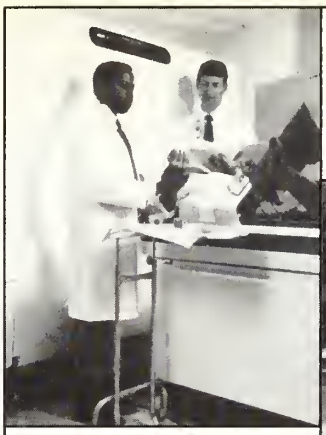

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- General Internists
- Geriatric Internists
- Pediatricians
- Urgent Care Physicians
- Anesthesiologists
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California: CIGNA Healthplans of CA, Physician Recruitment, 505 N. Brand Blvd., Suite 400-49, Glendale, CA 91203, (800) 468-9013.

Arizona: CIGNA Healthplan of AZ, Physician Recruitment, 11001 N. Black Canyon Hwy, Suite 400-49, Phoenix, AZ 85029, (800) 252-2471.

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(Continued from Page 549)

PHYSICIANS WANTED

FAMILY PRACTITIONER/INTERNIST PORTLAND, OREGON

Highly respected 35 member multispecialty group seeks Primary Care physician for one of its satellite clinics in the metro Portland area. Join four other Primary Care physicians in this growing suburban area of well-educated families and retirees. Call will be one in five. Portland offers an outstanding quality of life near mountains and the ocean with diverse cultural and educational opportunities. Housing is affordable and schools are excellent! Compensation is commensurate with experience. Excellent benefits package. **Call Pat Wall at (800) 462-1857 for more information.**

MEDICAL DIRECTOR/CLINICIAN

Family Practice, OB optional, opening July 1, 1993 for Berkeley Primary Care community clinic. Competitive salary, paid professional liability insurance, reasonable call requirements. Spacious, modern, fully equipped office. Accessible to the beautiful San Francisco bay area.

PLEASE CONTACT:

John Ford, MD
Berkeley Primary Care Access Clinic
PO Box 11406
Berkeley, CA 94701-2406
(510) 204-4624 or (510) 204-4536

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

TWO INVASIVE CARDIOLOGISTS AND FAMILY PHYSICIANS NEEDED. Unique opportunity. Gorgeous California central coast. Partnership within year. Send references/CV to PO Box 220, 395 Del Monte Center, Monterey, CA 93940.

MONTANA, IDAHO, WASHINGTON. Quality life and quality medicine combined. Primary Care and specialty openings. Wonderful place for family; low crime, drug, traffic problems. Outdoor recreation available at your door. Call or send CV to FHS, 4656 S Utah Ave, Butte, MT 59701; (406) 494-1448.

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NORTHWEST REGION

Physicians needed to join a multispecialty group, partnership, or solo practice, due to the explosive population growth. BC/BE physician specialties:

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- **PEDIATRICS**
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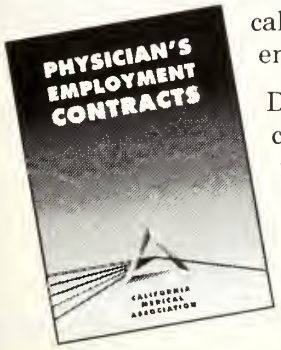

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California Medical Association—PO Box 7690, San Francisco 94120-7690. (415) 541-0900. Annual Meeting: March 18-23, 1994, Disneyland Hotel, Anaheim.

Colorado Medical Society—PO Box 17550, Denver 80217-0550. (303) 779-5455. Annual Meeting: September 10-12, 1993, Snowmass Village, Snowmass.

Hawaii Medical Association—1360 S Beretania, Honolulu 96814. (808) 536-7702. Annual Meeting: October 9-11, 1993, Ritz Carlton Kapalua, Maui.

Idaho Medical Association—305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 29-31, 1993, Sun Valley.

Montana Medical Association—2012 11th Ave, Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: September 30-October 2, 1993, Butte.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1994, date and location to be announced.

New Mexico Medical Society—7770 Jefferson NE, Suite 400, Albuquerque 87109. (505) 828-0237. Annual Meeting: May 14-15, 1993, Society Office, Albuquerque.

Utah Medical Association—540 E Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 22-25, 1993, University Park Hotel, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg, 2033 6th Ave, Seattle 98121. (206) 441-WSMA. Annual Meeting: September 9-12, 1993, Jantzen Beach, Oregon.

Wyoming Medical Society—PO Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 10-12, 1993, Jackson Lake Lodge, Moran.

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Zantac®

ranitidine HCl/Glaxo 150 mg and 300 mg tablets

ntac® 150 Tablets **BRIEF SUMMARY**
nitidine hydrochloride)
ntac® 300 Tablets
nitidine hydrochloride)
ntac® Syrup
nitidine hydrochloride)

e following is a brief summary only. Before prescribing, see complete prescribing information in ntac® product labeling

OICATIONS AND USAGE: Zantac® is indicated in
Short-term treatment of active duodenal ulcer
Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers
The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and sys-nic mastocytosis).
Short-term treatment of active, benign gastric ulcer
Treatment of gastroesophageal reflux disease (GERD).
Treatment of endoscopically diagnosed erosive esophagitis.
Concomitant antacids should be given as needed for pain relief to patients with active duodenal ul-; active, benign gastric ulcer; hypersecretory states, GERD, and erosive esophagitis.

NTRAINDICATIONS: Zantac® is contraindicated for patients known to have hypersensitivity to the ug or any of the ingredients

ECAUTIONS: General: 1. Symptomatic response to Zantac® therapy does not preclude the pres-ce of gastric malignancy
Since Zantac is excreted primarily by the kidney, dosage should be adjusted in patients with im-red renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients h hepatic dysfunction since Zantac is metabolized in the liver
Rare reports suggest that Zantac may precipitate acute porphyric attacks in patients with acute por-yria. Zantac should therefore be avoided in patients with a history of acute porphyria
boratory Tests: False-positive tests for urine protein with Multistix® may occur during Zantac ther-y, and therefore testing with sulfosalicylic acid is recommended.
ug Interactions: Although Zantac has been reported to bind weakly to cytochrome P-450 *in vitro*, ommended doses of the drug do not inhibit the action of the cytochrome P-450-linked oxygenase zymes in the liver. However, there have been isolated reports of drug interactions that suggest that ntac may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a -dependent effect on absorption or a change in volume of distribution)
ncreased or decreased prothrombin times have been reported during concurrent use of ranitidine d warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg day, no interaction occurred, ranitidine had no effect on warfarin clearance or prothrombin time e possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg per day has been investigated.
rcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or cinogenic effects in life-span studies in mice and rats at dosages up to 2,000 mg/kg per day.
Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for muta-nicity at concentrations up to the maximum recommended for these assays.
In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the come of two matings per week for the next 9 weeks.
egnancy: ***Teratogenic Effects: Pregnancy Category B:*** Reproduction studies have been performed rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of im-red fertility or harm to the fetus due to Zantac. There are, however, no adequate and well-controlled dies in pregnant women. Because animal reproduction studies are not always predictive of human ponse, this drug should be used during pregnancy only if clearly needed
rsing Mothers: Zantac is secreted in human milk. Caution should be exercised when Zantac is ad-nistered to a nursing mother.
diatric Use: Safety and effectiveness in children have not been established
e in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years of age) were no different m those in younger age-groups. The incidence rates for adverse events and laboratory abnormali-s were also not different from those seen in other age-groups.

VERSE REACTIONS: The following have been reported as events in clinical trials or in the routine nagement of patients treated with Zantac®. The relationship to Zantac therapy has been unclear in ny cases. Headache, sometimes severe, seems to be related to Zantac administration
ntral Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases eversible mental confusion, agitation, depression, and hallucinations have been reported, predom-ntly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in commodation have been reported. Rare reports of reversible involuntary motor disturbances have en received.
diovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, brady-dia, atrioventricular block, and premature ventricular beats
strointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare re-ts of pancreatitis
patic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in

Zantac® 150 and 300 (ranitidine hydrochloride) Tablets
Zantac® (ranitidine hydrochloride) Syrup

6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be im-mediately discontinued. These events are usually reversible, but in exceedingly rare circumstances death has occurred
Musculoskeletal: Rare reports of arthralgias and myalgias
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have oc-curred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired im-mune hemolytic anemia have been reported
Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hor-mone by Zantac and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Zantac has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Zantac, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases suggestive of mild erythema multiforme, and, rarely, alopecia
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), ana-phylaxis, angioneurotic edema, and small increases in serum creatinine

OVERDOSAGE: There has been limited experience with overdosage. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in nor-mal clinical experience (see ADVERSE REACTIONS). In addition, abnormalities of gait and hypoten-sion have been reported

When overdosage occurs, the usual measures to remove unabsorbed material from the gastroin-testinal tract, clinical monitoring, and supportive therapy should be employed

Studies in dogs receiving dosages of Zantac® in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively

DOSAGE AND ADMINISTRATION: (See complete prescribing information in Zantac® product labeling.)
Active Duodenal Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 tea-spoonfuls equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL (4 teaspoonfuls equivalent to 300 mg of ranitidine) once daily at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated
Maintenance Therapy: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoon-fuls equivalent to 150 mg of ranitidine) at bedtime
Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recom-mended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer Zantac® 150-mg doses more fre-quently. Dosages should be adjusted to individual patient needs, and should continue as long as clini-cally indicated. Dosages up to 6 g per day have been employed in patients with severe disease.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoon-fuls equivalent to 150 mg of ranitidine) twice a day
GERD: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) twice a day.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL (2 teaspoon-fuls equivalent to 150 mg of ranitidine) four times a day
Dosage Adjustment for Patients With Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with Zantac, the recommended dosage in patients with a creatinine clearance less than 50 mL per minute is 150 mg or 10 mL (2 teaspoonfuls equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the fre-quency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis re-duces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis

July 1992
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IN HYPERTENSION—

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Calan® SR
Verapamil HCl
SUSTAINED-RELEASE CAPLETS

THE GENTLE GIANT

Make It Your Choice
for a Lifetime—write DAW.

The recommended starting dosage for Calan SR is 180 mg once daily. Dose titration will be required in some patients to achieve blood pressure control. A lower starting dosage of 120 mg/day may be warranted in some patients (eg, the elderly, patients of small stature). Dosages above 240 mg daily should be administered in divided doses. Calan SR should be administered with food. Constipation, which is easily managed in most patients, is the most commonly reported side effect of Calan SR.

BRIEF SUMMARY

Contraindications: Severe LV dysfunction (see *Warnings*), hypotension (systolic pressure < 90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block (if no pacemaker is present), atrial flutter/fibrillation with an accessory bypass tract (eg, WPW or LGL syndromes), hypersensitivity to verapamil.

Warnings: Verapamil should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%) or moderate to severe symptoms of cardiac failure and in patients with any degree of ventricular dysfunction if they are receiving a beta-blocker. Control milder heart failure with optimum digitalization and/or diuretics before Calan SR is used. Verapamil may occasionally produce hypotension. Elevations of liver enzymes have been reported. Several cases have been demonstrated to be produced by verapamil. Periodic monitoring of liver function in patients on verapamil is prudent. Some patients with paroxysmal and/or chronic atrial flutter/fibrillation and an accessory AV pathway (eg, WPW or LGL syndromes) have developed an increased antegrade conduction across the accessory pathway bypassing the AV node, producing a very rapid ventricular response or ventricular fibrillation after receiving i.v. verapamil (or digitalis). Because of this risk, oral verapamil is contraindicated in such patients. AV block may occur (2nd- and 3rd-degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with verapamil.

Precautions: Verapamil should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Verapamil may decrease neuromuscular transmission in patients with Duchenne's muscular dystrophy and may prolong recovery from the neuromuscular blocking agent vecuronium. It may be necessary to decrease verapamil dosage in patients with attenuated neuromuscular transmission. Combined therapy with beta-adrenergic blockers and verapamil may result in additive negative effects on heart rate, atrioventricular conduction and/or cardiac contractility; there have been reports of excessive bradycardia and AV block, including complete heart block. The risks of such combined therapy may outweigh the benefits. The combination should be used only with caution and close monitoring. Decreased metoprolol and propranolol clearance may occur when either drug is administered concomitantly with verapamil. A variable effect has been seen with combined use of atenolol. Chronic verapamil treatment can increase serum digoxin levels by 50% to 75% during the first week of therapy, which can result in digitalis toxicity. In patients with hepatic cirrhosis, verapamil may reduce total body clearance and extrarenal clearance of digitoxin. The digoxin dose should be reduced when verapamil is given, and the patient carefully monitored. Verapamil will usually have an additive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after verapamil administration. Concomitant use of flecainide and verapamil may have additive effects on myocardial contractility, AV conduction, and repolarization. Combined verapamil and quinidine therapy in patients with hypertrophic cardiomyopathy should be avoided, since significant hypotension may result. Concomitant use of lithium and verapamil may result in an increased sensitivity to lithium (neurotoxicity), with either no change or an increase in serum lithium levels; however, it may also result in a lowering of serum lithium levels. Patients receiving both drugs must be monitored carefully. Verapamil may increase carbamazepine concentrations during combined use. Rifampin may reduce verapamil bioavailability. Phenobarbital may increase verapamil clearance. Verapamil may increase serum levels of cyclosporin. Verapamil may inhibit the clearance and increase the plasma levels of theophylline. Concomitant use of inhalation anesthetics and calcium antagonists needs careful titration to avoid excessive cardiovascular depression. Verapamil may potentiate the activity of neuromuscular blocking agents (curare-like and depolarizing); dosage reduction may be required. There was no evidence of a carcinogenic potential of verapamil administered to rats for 2 years. A study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. Pregnancy Category C. There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. Verapamil is excreted in breast milk; therefore, nursing should be discontinued during verapamil use.

Adverse Reactions: Constipation (7.3%), dizziness (3.3%), nausea (2.7%), hypotension (2.5%), headache (2.2%), edema (1.9%), CHF, pulmonary edema (1.8%), fatigue (1.7%), dyspnea (1.4%), bradycardia: HR < 50/min (1.4%), AV block: total 1°,2°,3° (1.2%), 2° and 3° (0.8%), rash (1.2%), flushing (0.6%), elevated liver enzymes, reversible non-obstructive paralytic ileus. The following reactions, reported in 1.0% or less of patients, occurred under conditions where a causal relationship is uncertain: angina pectoris, atrioventricular dissociation, chest pain, claudication, myocardial infarction, palpitations, purpura (vasculitis), syncope, diarrhea, dry mouth, gastrointestinal distress, gingival hyperplasia, ecchymosis or bruising, cerebrovascular accident, confusion, equilibrium disorders, insomnia, muscle cramps, paresthesia, psychotic symptoms, shakiness, somnolence, arthralgia and rash, exanthema, hair loss, hyperkeratosis, macules, sweating, urticaria, Stevens-Johnson syndrome, erythema multiforme, blurred vision, gynecomastia, galactorrhea/hyperprolactinemia, increased urination, spotty menstruation, impotence.

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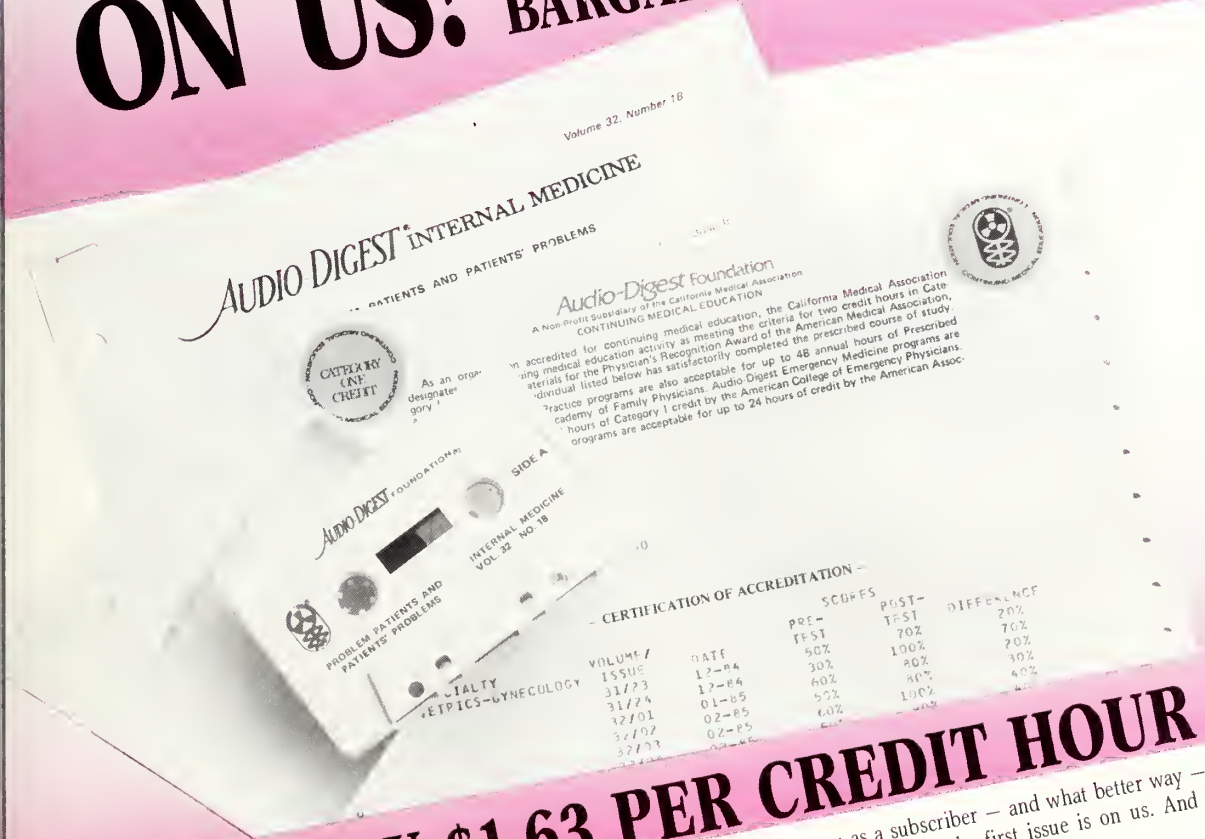

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Breast of chicken

3-oz. cooked serving of chicken breast

Best of pork

3-oz. cooked serving of pork tenderloin

Today's Pork: Compare it to chicken for a healthy surprise

You may not have considered pork to be a healthy choice for your patients on fat-modified diets. But today's fresh pork compares surprisingly well to chicken in total fat, saturated fat, cholesterol, and calories.[1,2*]

Compare pork with chicken[1,2*]

	Calories	Total Fat	Saturated Fatty Acids	Cholesterol
Chicken Breast, skinless	140	3.0 g	0.9 g	72 mg
Pork Tenderloin, trimmed	139	4.1 g	1.4 g	67 mg
Pork Top Loin Roast (boneless), trimmed	165	6.1 g	2.2 g	66 mg
Center Loin Chop, trimmed	172	6.9 g	2.5 g	70 mg
Chicken Thigh, skinless	178	9.2 g	2.6 g	81 mg

*Table refers to 3-oz, cooked servings.

New study: Pork is now 31% leaner

Pork is leaner today because of significant changes made in breeding and feeding techniques.[1] According to new 1992 official USDA data, fresh pork sold today contains an average of 31% less fat after cooking and trimming than the same pork cuts reported in 1983.[1]

Today's pork fits well within the dietary guidelines recommended by both the American Heart Association and the National Cholesterol Education Program. Here's some advice to help patients on low-fat diets enjoy the variety, extra taste, and versatility of pork:

- Choose the leanest cuts. Shop for cuts with "loin" in the name.
- Trim away any visible fat.
- Keep portions moderate (about 3 oz, cooked).
- Prepare by broiling or roasting, and avoid additional fat in preparation.

1. US Dept of Agriculture. *Composition of Foods: Pork Products*, 1992. Agricultural handbook 8-10.
2. US Dept of Agriculture. *Composition of Foods: Poultry Products*, 1979. Agricultural handbook 8-5.

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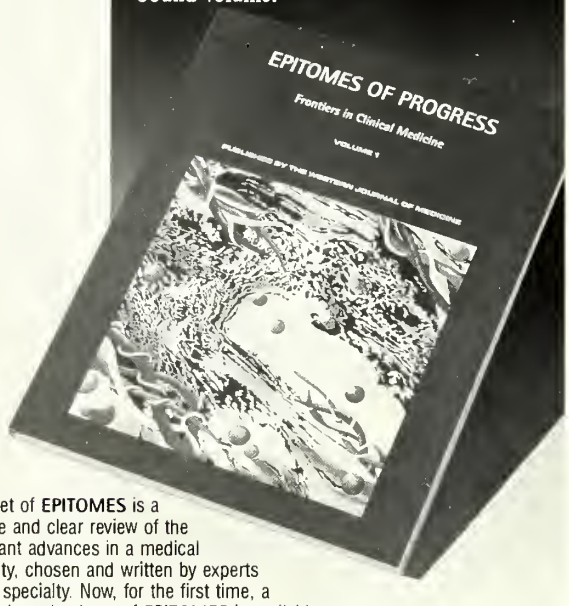

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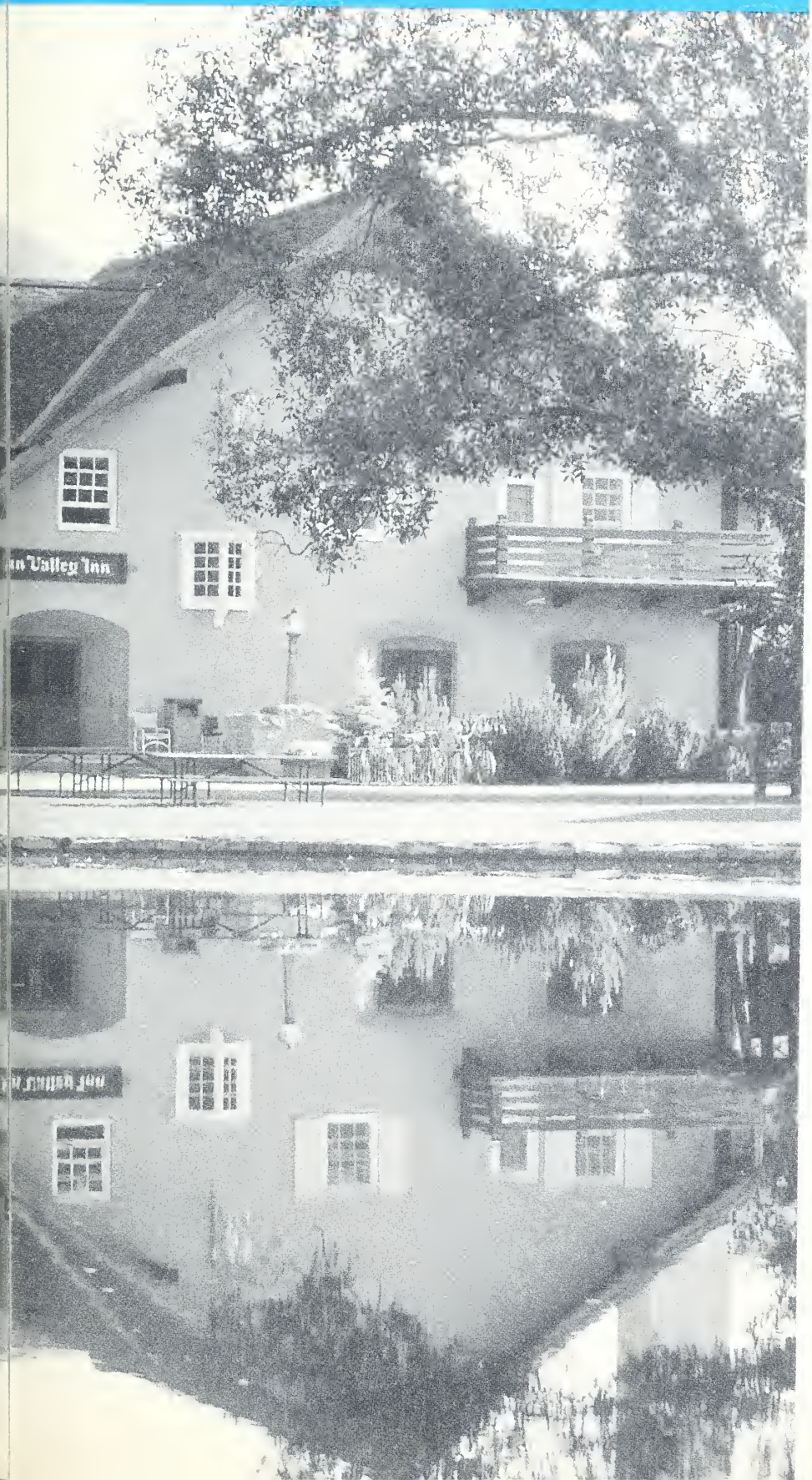

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SCIENTIFIC SESSION

Friday, July 30, 1993

7:00 am	TECHNICAL EXHIBITS OPEN CONTINENTAL BREAKFAST
7:15 am	WELCOME—Joe Daglen, MD, IMA President
7:30-8:30 am	SCUBA DIVING INJURIES Ken Kizer, MD
8:30-9:30 am	RURAL HEALTH ISSUES AND THE CLINTON ADMINISTRATION David A. Kindig, MD, PhD
9:30 am	RECESS TO VIEW EXHIBITS
10:00-11:00 am	ANIMAL ENCOUNTERS Ken Kizer, MD
11:00-noon	TICK-BORNE DISEASES Douglas Gentile, MD
12:00 lunch-1:30	JOIN AUXILIARY RECOGNIZING DOMESTIC VIOLENCE Susan Hadley
1:30-2:30 pm	TAKING CHILDREN INTO THE WILDERNESS Barbra Kennedy, MD, and Douglas Gentile, MD
2:30-3:30 pm	MUSHROOM INGESTION DISEASES Jim Blackman, MD

Saturday, July 31, 1993

10:00 am	HEALTH CARE REFORM—THE OREGON PLAN John Kitzhaber, MD, Former Senator from Oregon

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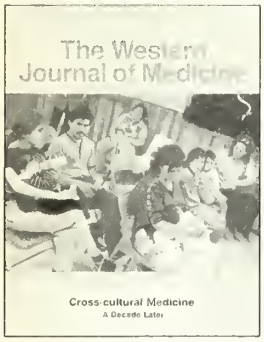

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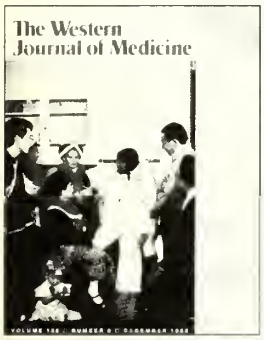

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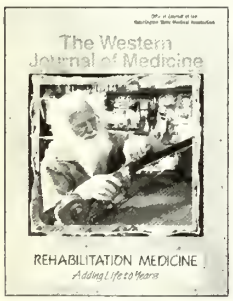

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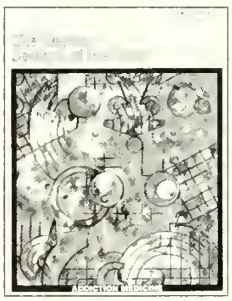

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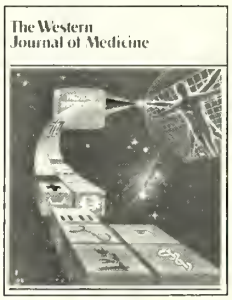

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Usage In Children: Since there is no experience in children who have received this drug, safety and efficacy in children have not been established.

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Dihydrocodeine can produce drug dependence of the codeine type and therefore has the potential of being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of dihydrocodeine, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications.

OVERDOSAGE: Dihydrocodeine: Signs and Symptoms: Serious overdose with DHC Plus™ is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including codeine. Therefore, an appropriate dose of naloxone hydrochloride should be administered, preferably by the intravenous route and simultaneously with efforts at respiratory resuscitation. Since the duration of action of dihydrocodeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration.

The antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated.

Gastric emptying may be useful in removing unabsorbed drug.

Acetaminophen: Signs and Symptoms: In acute acetaminophen overdosage, dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and thrombocytopenia may also occur. In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams and fatalities with less than 15 grams. Importantly, young children seem to be more resistant than adults to the hepatotoxic effect of an acetaminophen overdose. Despite this, the measures outlined below should be initiated in any adult or child suspected of having ingested an acetaminophen overdose.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

Treatment: The stomach should be emptied promptly by lavage or by induction of emesis with syrup of ipecac. Patients' estimates of the quantity of a drug ingested are notoriously unreliable. Therefore, if an acetaminophen overdose is suspected, a serum acetaminophen assay should be obtained as early as possible, but no sooner than four hours following ingestion. Liver function studies should be obtained initially and repeated at 24-hour intervals.

The antidote, N-acetylcysteine, should be administered as early as possible, preferably within 16 hours of the overdose ingestion for optimal results, but in any case within 24 hours. Following recovery, there are no residual, structural or functional hepatic abnormalities.

DOSAGE AND ADMINISTRATION: Dosage should be adjusted according to the severity of the pain and the response of the patient. DHC Plus™ is given orally. The usual adult dosage is two capsules every (4) hours as needed for pain.

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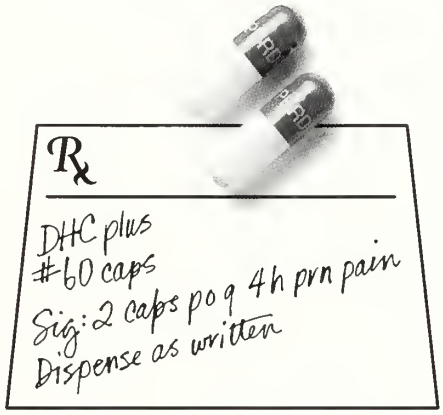

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ABSTRACTS JUNE 1993

(Tong MJ, Co RL, Bellak C: Hepatitis A vaccination. West J Med 1993; 158:602-605)

The safety and immunogenicity of an inactivated hepatitis A virus vaccine were assessed in 101 healthy adults. Seronegative persons with normal serum aminotransferase levels were grouped according to age: Group 1 (n = 24) and group 3 (n = 22) were between 18 and 40 years of age, and group 2 (n = 25) and group 4 (n = 30) were older than 40 years. Groups 1 and 2 received vaccine on a 0-, 1-, and 2-month schedule (schedule A), and groups 3 and 4 received the vaccine on a 0-, 1-, and 12-month schedule (schedule B). Of the 101 vaccinated subjects, 98 (97%) seroconverted with antibody titers to hepatitis A virus of ≥20 IU per liter after the first dose, and all subjects seroconverted after the second dose. The geometric mean titers a month after the third vaccine dose were significantly greater ($P < .03$) on both schedules for younger subjects (schedule A, 1,743 IU per liter, and schedule B, 7,882 IU per liter) than for older subjects (schedule A, 826 IU per liter, and schedule B, 4,279 IU per liter). Also, the differences in geometric mean titers a month after the third dose were significantly greater ($P < .001$) for subjects in both age groups on schedule B (group 3, 7,882 IU per liter, and group 4, 4,279 IU per liter) than for those in schedule A (group 1, 1,743 IU per liter, and group 2, 826 IU per liter). The hepatitis A virus vaccine was well tolerated, with mild discomfort at the injection site being the main side effect. This vaccine is both safe and highly immunogenic.

HEPATITIS A VIRUS **HAV VACCINATION**

(Tong MJ, Co RL, Bellak C: Hepatitis A vaccination. West J Med 1993; 158:602-605)

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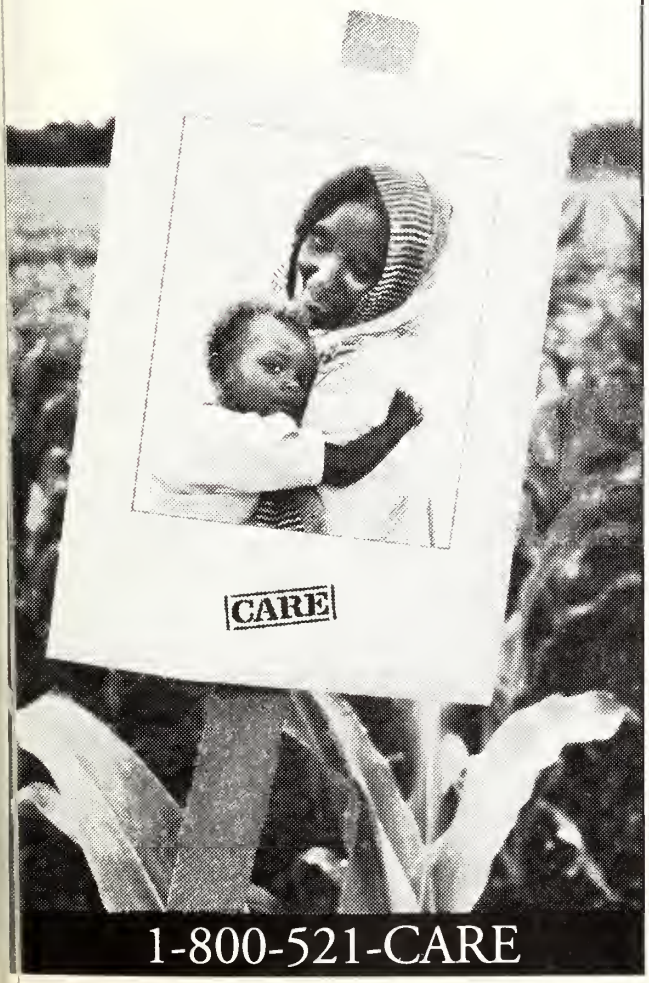

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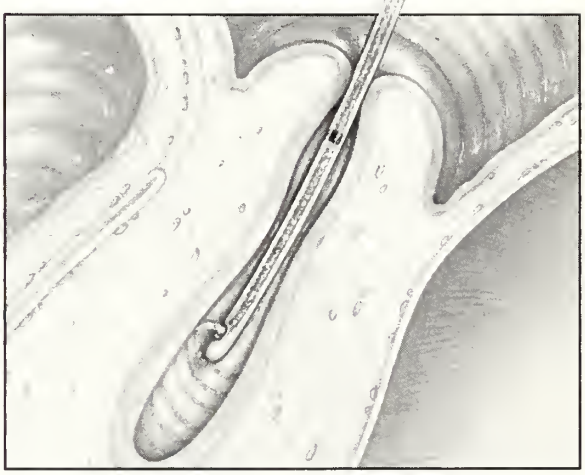

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ALLERGY/IMMUNOLOGY

September 30-October 2—**1st International Conference on Engineered Vaccines for Cancer and AIDS.** St Francis Memorial Hospital and Northern California Melanoma Center at Fairmont Hotel, San Francisco. Thurs-Sat. Contact: Cass Jones, 7916 Convoy Ct, San Diego 92111. (619) 565-9921.

ANESTHESIOLOGY

September 11-12—**Case Conference in Anesthesia.** California Society of Anesthesiology at Hyatt Hotel, Fisherman's Wharf, San Francisco. Sat-Sun. 9 hrs. $195. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

October 17-23—**Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiologists at Four Seasons Hotel, Wailea, Maui, Hawaii. Sun-Sat. 23 hrs. $425. Contact: CSA, 1065 E Hillsdale Blvd, Ste 410, Foster City 94404. (800) 345-3691.

November 12-14—**Anesthesiology Update: 1993.** UCD at Monterey Plaza. Fri-Sun. Contact: UCD.

November 19-20—**3rd Annual Pain Management.** UCD at Silverado Country Club, Napa. Fri-Sat. Contact: UCD.

CARDIOLOGY

July 18-22—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, Nevada. Sun-Thurs. 19 hrs. $400. Contact: UCD.

August 5-7—**Critical Care Cardiology.** UCSF at Sheraton Palace Hotel, San Francisco. Thurs-Sat. 16 hrs. Contact: UCSF.

September 7-10—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Tues-Fri. 24 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, 403C, La Jolla 92037. (619) 554-8556.

October 1-3—**Coronary Interventions: 1993.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Fri-Sun. 14 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 14-16—**Cardiology Update: 1993.** UCSF at Quail Lodge Resort and Conference Center, Carmel. Thurs-Sat. 12 hrs. $445. Contact: UCSF.

CARDIOVASCULAR DISEASE

June 18-20—**Diagnosis and Management of Respiratory Diseases.** Medical Education Resources at Marriott Hotel, Monterey. Fri-Sun. 12 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

June 25-27—**Preventive Cardiovascular Medicine: Challenge for the '90s.** UCLA at Universal City Hilton and Towers, Universal City. Fri-Sun. 17.5 hrs. $175. Contact: UCLA Extension.

September 28-October 1—**47th Annual Fall Conference and Scientific Sessions of the Council for High Blood Pressure Research.** American Heart Association at Hyatt Regency, San Francisco. Tues-Fri. 21 hrs. Contact: AHA, 7272 Greenville Ave, Dallas, TX 75231. (214) 706-1511.

DERMATOLOGY

July 20-24—**Superficial Anatomy and Cutaneous Surgery.** Scripps Clinic and Research Foundation and UCSD at UCSD Campus, San Diego. Tues-Sat. 36 hrs. $1100. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

July 29-31—**Workshop in Dermatopathology.** Scripps Clinic and Research Foundation at Sheraton Grande Torrey Pines Hotel, La Jolla. Thurs-Sat. 20 hrs. $435. Contact: James Graham, MD, Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

August 9-11—**Dermatology for the Non-Dermatologist.** Continuing Medical Education Associates at Hotel del Coronado, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

EMERGENCY MEDICINE

June 21-25—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

August 16-20—**Emergency Medicine Symposium II.** UCSD. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 15-17—**Advances in Emergency Medicine.** UCSD at Hyatt Regency, La Jolla. Fri-Sun. 20 hrs. $450. Contact: UCSD.

October 18-22—**Emergency Medicine Symposium I.** UCSD at San Diego Hilton Beach and Tennis Resort. Mon-Fri. 32 hrs. $495. Contact: UCSD.

October 21-23—**Traumatic Brain Injury.** UCD at Hilton Hotel, Sacramento. Thurs-Sat. Contact: UCD.

November 8-12—**Emergency Medicine Symposium III.** UCSD at San Diego Hilton. Mon-Fri. 32 hrs. $495. Contact: UCSD.

FAMILY PRACTICE/PRIMARY CARE

June 13-18—**17th Annual Fingers to the Toes: Primary Care Orthopaedics.** UCD at Stanford Sierra Camp, Fallen Leaf Lake. Sun-Fri. 26 hrs. $495. Contact: UCD.

June 24-27—**Primary Care Sports Medicine Conference.** UCLA at Hyatt Newporter, Newport Beach. Thurs-Sat. 20 hrs. $375. Contact: UCLA Extension.

July 5-8—**Family Practice Board Review Course.** UCSF at Hotel Nikko, San Francisco. Mon-Thurs. 25 hrs. $400. Contact: UCSF.

July 22-24—**Primary Care for the 21st Century.** UCSD at Catamaran Resort Hotel, San Diego. Thurs-Sat. 17 hrs. $250. Contact: UCSD.

August 6-8—**Cardiology for the Family Physician and Internist.** Continuing Medical Associates at Hotel del Coronado, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Office Gynecology for the Primary Care Physician.** SDSU at Hyatt Islandia, San Diego. Fri-Sun. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

August 20-22—**Primary Care Medicine: A Practical Approach.** Scripps Clinic at Le Meridien San Diego. Fri-Sun. 16 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

October 6-8—**Primary Care Medicine: Principles and Practice.** UCSF at Nikko Hotel, San Francisco. Wed-Fri. 20 hrs. $485. Contact: UCSF.

October 6-9—**15th Semiannual Wound Management Workshop for Primary Care.** UCSD at San Diego Hilton. 17 hrs. $475. Contact: UCSD.

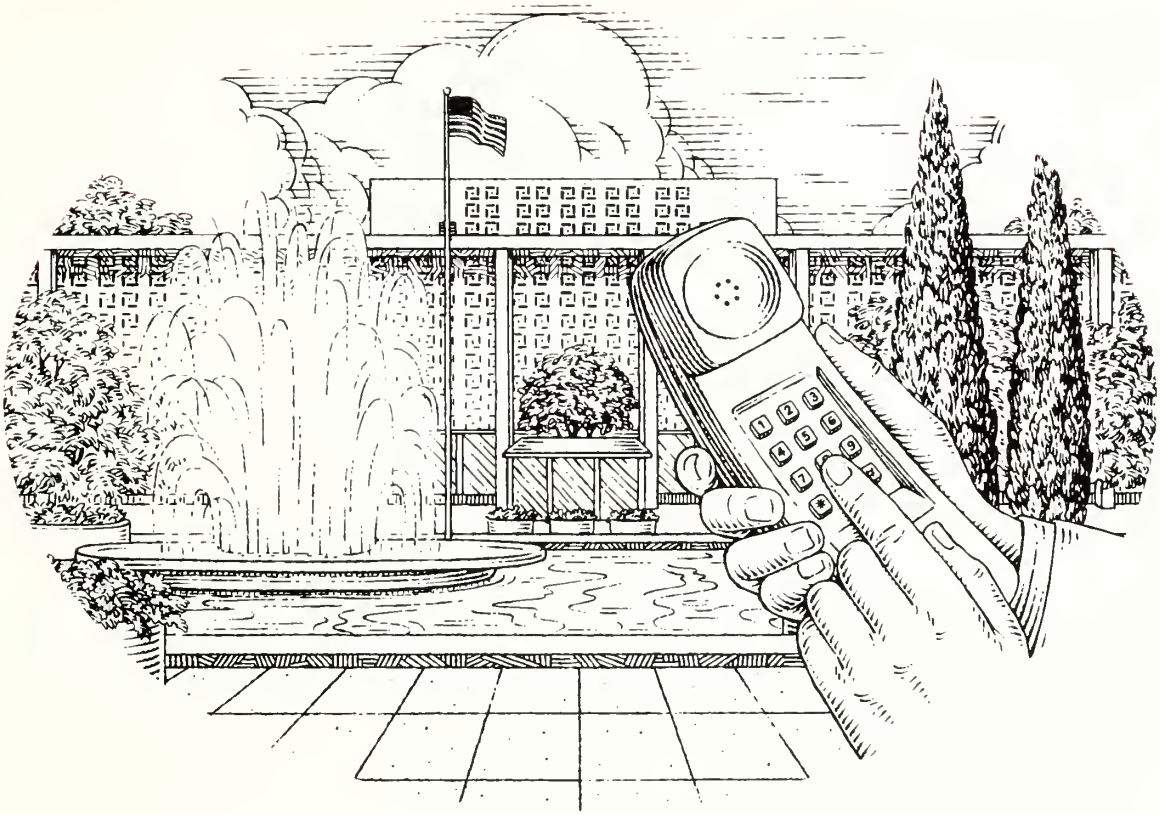
November 10-13—**North American Primary Care Research Group—Research Frontiers in Primary Care and Prevention.** UCSD at Hyatt Islandia on Mission Bay, San Diego. Wed-Sat. 23 hrs. $400. Contact: UCSD.

GERIATRICS

June 18—**La Familia Latino: Meeting the Needs of Latino Elders.** UCLA at Law School. Fri. 5 hrs. $115. Contact: UCLA Extension.

November 8-10—**Geriatrics Update: 1993.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Mon-Wed. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 570)



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INFECTIOUS DISEASES

September 2-5—**HIV, AIDS, and Women.** UCSD at La Jolla Marriott. Thurs-Sun. 15 hrs. $200. Contact: UCSD.

November 5-7—**Advances in Infectious Disease.** Sharp Memorial Hospital at Loew's Coronado Bay Resort, San Diego. Fri-Sun. 20 hrs. $425. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 1-3—**Gastroenterology: Advances in Diagnosis and Management.** UCSF at Ana Hotel, San Francisco. Fri-Sun. 18 hrs. $430. Contact: UCSF.

October 14-16—**Recent Advances in Pulmonary and Critical Care Medicine.** UCSF at Ana Hotel, San Francisco. Thurs-Sat. 16 hrs. $415. Contact: UCSF.

INTERNAL MEDICINE

June 22-25—**Advances in Internal Medicine.** UCSF at Cole Hall, San Francisco. Tues-Fri. 33 hrs. $630. Contact: UCSF.

August 22-27—**New Advances in Internal Medicine.** UCD at Hyatt Regency, Monterey. Sun-Fri. Contact: UCD.

November 12-13—**Clinical Applications of New Advances in Internal Medicine.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. Contact: UCD.

NEUROLOGY

August 5-7—**5th Annual New Advances in Common Neurological Disorders.** UCSD at Catamaran Hotel, San Diego. 14 hrs. $350. Contact: UCSD.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, PO Box 7690, San Francisco 94120-7690. (415) 541-0900.

CPMC: California Pacific Medical Center
Contact: Continuing Education, California Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 923-3441.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Herbert M. Thomas, MD, MPH, Director of CME, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th St, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: James J. Couperus, MD, Associate Dean for Educational Affairs, Loma Linda University School of Medicine, Loma Linda 92350.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Medical School Office Building, Suite X-365, Stanford 94305-6114. (415) 723-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, 2701 Stockton Blvd, Sacramento 95817. (916) 734-5390.

UCI: University of California, Irvine
Contact: Melvin I. Marks, MD, Director, Memorial/UCI Center for Health Education, Long Beach Memorial Medical Center, 2801 Atlantic Ave, PO Box 1428, Long Beach, California 90801-1428. (213) 595-3811.

UCLA: University of California, Los Angeles Extension
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (310) 825-8423.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 534-3940.

UCSF: University of California, San Francisco
Contact: Janet Johnson, Administrative Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 476-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 1975 Zonal Ave, KAM314, Los Angeles 90033. (800) 872-1119.

OB/GYN

November 20—**Infertility Update VII.** Scripps Clinic and Research Foundation, La Jolla. Sat. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

OCCUPATIONAL/ENVIRONMENTAL

July 26-30—**Sports Medicine 1993.** UCSD at San Diego Princess Resort. Mon-Fri. 21 hrs. $350. Contact: UCSD.

October 25-29—**Occupational and Environmental Medicine.** UCSF at Miyako Hotel, San Francisco. Mon-Fri. 40 hrs. $700. Contact: UCSF.

ONCOLOGY

October 25-27—**17th Annual Cancer Symposium.** Scripps Memorial Hospital at Sheraton Harbor Island Hotel, San Diego. Mon-Wed. 20 hrs. $390. Contact: Cancer Symposium Conference Office, PO Box 16502, Irvine 92713-6338. (800) 321-6338.

November 5-6—**American College of Surgeons: Cancer Management Course.** UCD at Cancer Center Auditorium, Sacramento. Fri-Sat. 13 hrs. $400. Contact: UCD.

OPHTHALMOLOGY

September 18—**General Medicine Update for Ophthalmologists.** UCD at Cancer Center Auditorium, Sacramento. Sat. Contact: UCD.

October 16—**Annual Ophthalmology Update: 1993.** UCD at Cancer Auditorium at Sacramento. Sat. Contact: UCD.

ORTHOPAEDICS

June 16-19—**10th Annual San Diego Shoulder Arthroscopy Meeting.** Tri-City Orthopaedics at Hyatt Regency Hotel, La Jolla. Wed-Sat. Contact: Rebecca Rimmer, 3905 Waring Rd, Oceanside 92056. (619) 940-2066.

July 25-31—**An Update in Orthopaedics.** Kaiser Permanente at Hyatt Wailea, Maui, Hawaii. Sun-Sat. 20 hrs. $395-$495. Contact: Scott Waters, 1800 Harrison, 20th Fl, Oakland 94612. (510) 987-3087.

October 18-20—**The Knee and Shoulder in Sports.** American College of Sports Medicine at Westin Maui, Kaanapali Beach, Maui, Hawaii. Mon-Wed. 13 hrs. $300. Contact: Stuart Zeman, MD. (800) 346-3277.

OTOLARYNGOLOGY

June 23-25—**20th International Conference on Cochlear Implants.** UCSF at Ritz-Carlton, San Francisco. Wed-Fri. Contact: UCSF.

November 4-6—**The San Francisco Otology, Neurotology, and Skull Base Surgery Update—1993.** UCSF at Ritz-Carlton Hotel, San Francisco. Thurs-Sat. 22 hrs. $395. Contact: UCSF.

PATHOLOGY

August 7-14—**14th Annual Comprehensive Fine Needle Biopsy Course.** UCSF at Ritz-Carlton, Kapalua, Maui, Hawaii. 1 wk. 27 hrs. $950. Contact: UCSF.

October 2—**33rd Annual Scientific Symposium on Kidney Disease.** National Kidney Foundation of Southern California at Stouffer Esmeralda Resort, Indian Wells. Sat. Contact: Sylvie Tarro, (310) 641-8152.

October 25-29—**19th Annual Lukes Conference: Diagnostic Approaches to Lymphoproliferative Disorders.** Fri-Tues. 27 hrs. Contact: Scripps Clinic, 10666 N Torrey Pines Rd, La Jolla 92037. (619) 554-8556.

PEDIATRICS

August 23-25—**Pediatrics Update: 1993.** SDSU at Hyatt Islandia, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

PSYCHIATRY

June 23-25—**Treatment of the Sexual Problems of Adults Molested as Children.** UCLA at Beverly Hilton Hotel. Wed-Fri. 19.5 hrs. $250-$395. Contact: UCLA Extension.

(Continued on Page 576)

CONTINUING MEDICAL EDUCATION CALENDAR

The Southern Medical Association is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians.

JUNE 25-27, 1993

SOUTHERN ASSOCIATION FOR GERIATRIC MEDICINE, THIRD ANNUAL MEETING
LOCATION: The Ritz-Carlton, Naples, Florida
SPECIALTY: Primary Care, Geriatrics, Internal Medicine
CME CREDIT: CAT I-13; AAFP 13 Prescribed; AOA 13 CAT 2A
FEE: SMA/SAGM Member-$295; Nonmember-$470; Nonphysician-$200

JULY 9-11, 1993

THIRD ANNUAL OFFICE MANAGEMENT OF INFECTIOUS DISEASES
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Gynecology, Pediatrics
CME CREDIT: CAT I-15; AAFP 15.25 Prescribed; ACOG 15 Cognates; AOA 15.5 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 19-22, 1993

SECOND ANNUAL SURGERY UPDATE
LOCATION: The Cloister, Sea Island, Georgia
SPECIALTY: General Surgery
CME CREDIT: CAT I-14
FEE: SMA Member-$400; Nonmember-$525; Nonphysician-$250

JULY 22, 1993

FEES AND CLAIMS ANALYSIS TECHNIQUES
LOCATION: The Cloister, Sea Island, Georgia
FEE: SMA Member or Employee-$195; Nonmember or Employee-$295

JULY 23-24, 1993

IMPROVING YOUR PRACTICE PRODUCTIVITY AND PERFORMANCE
LOCATION: The Cloister, Sea Island, Georgia
FEE: SMA Member or Employee-$195; Nonmember or Employee-$295

JULY 26-29, 1993

FOCUS ON THE FEMALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Ob/Gyn, Primary Care
CME CREDIT: CAT I-18; AAFP 18 Prescribed; ACOG 19 Cognates; AOA 18 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

JULY 30-AUGUST 1, 1993

FOCUS ON THE MALE PATIENT
LOCATION: Kiawah Island Resort, Kiawah Island, South Carolina (Near Charleston)
SPECIALTY: Primary Care, Urology
CME CREDIT: CAT I-14; AAFP 13 Prescribed; AOA 14 CAT 2A
FEE: SMA Member-$295; Nonmember-$420; Nonphysician-$200

AUGUST 27-29, 1993

FAMILY MEDICINE UPDATE
LOCATION: Callaway Gardens, Pine Mountain, Georgia
SPECIALTY: Primary Care, Family Practice
CME CREDIT: CAT I-14, AAFP 14 Prescribed; AOA 14 CAT 2A
FEE: SMA Member-$295; Nonmember-$470

OCTOBER 28-31, 1993

SOUTHERN MEDICAL ASSOCIATION'S 87TH ANNUAL SCIENTIFIC ASSEMBLY
LOCATION: New Orleans Convention Center, New Orleans, Louisiana
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- 19 Joint Specialty Section Meetings
- 34 Postgraduate Courses
- 15 Clinical and Scientific Symposia
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(Continued from Page 562)

612 Treatment and Prevention of Milk Allergy
STANLEY P. GALANT, MD

613 Exercise-Induced Asthma and Anaphylaxis
HAROLD S. NOVEY, MD

613 Antihistamines and the Heart
DIANA MARQUARDT, MD

614 Vocal Cord Dysfunction Presenting as Asthma
WILLIAM SOKOL, MD

615 Sinusitis
ROBERT C. BOCIAN, MD, PhD

616 Topical Nasal Steroids for Allergic Rhinitis
MICHAEL J. WELCH, MD

617 Latex Allergy
ALAN B. GOLDSOBEL, MD

ALERTS, NOTICES, AND CASE REPORTS

619 Tularemia From Domestic Cats
W. CONRAD LILES, MD, PhD, and RICHARD J. BURGER, MD

From the Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington School of Medicine, Seattle. Dr Burger is in private practice in Fairbanks, Alaska.

622 Babesiosis in California
ANTHONY F. JERANT, MD, and ALFRED D. ARLINE, MD

From the Department of Family Practice, Madigan Army Medical Center, Tacoma, Washington.

625 Rocky Mountain Spotted Fever Following Cardiac Transplantation
TENA M. RALLIS, MD; JOHN D. KRIESEL, MD; J. STEPHEN DUMLER, MD; LYNNE E. WAGONER, MD; E. DAVID WRIGHT, MD; and SPOTSWOOD L. SPRUANCE, MD

From the Department of Medicine, Divisions of Dermatology, Infectious Diseases, and Cardiology, University of Utah School of Medicine, Salt Lake City, and the Department of Pathology, University of Texas Medical Branch at Galveston.

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629 Way of the Healer—The Work of Healing and the Healing of Work
WILLIAM B. STEWART, MD

From the Program in Medicine and Philosophy, Division of Education, California Pacific Medical Center, San Francisco.

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631 On 'Downsizing' Health Care
MALCOLM S. M. WATTS, MD

Dr Watts is Editor Emeritus, The Western Journal of Medicine, *San Francisco, California.*

631 Hansen's Disease—A Time for Cautious Optimism
RICHARD A. MILLER, MD

Dr Miller is Assistant Professor of Medicine, University of Washington School of Medicine, and Chief, Infectious Disease Section, Department of Veterans Affairs Medical Center, Seattle.

(Continued on Page 578)

A source of strength in a world of resistance

CEFOBID® 1g/2g q12h

(cefoperazone sodium) IM/IV

Please see adjacent page for brief summary of prescribing information.

CEFOBID® (cefoperazone sodium) has maintained in vitro activity over time

- An excellent *in vitro* susceptibility profile against the most common nosocomial pathogens[1-3]

Pseudomonas aeruginosa[2,3]		*Staphylococcus aureus*[2,3]	
1985	1990	1985	1990
91.0%	93.1%	92.0%	91.3%
(n=388)	(n=15,439)	(n=369)	(n=2,554)

From a retrospective, multicenter susceptibility data base; n=number of isolates; percent susceptible calculated with 95% confidence limits.

In vitro activity does not necessarily imply a correlation with *in vivo* results.

- An established record of clinical effectiveness in nosocomial pneumonia,* in complicated UTI,* and for approved indications in the febrile neutropenic patient*[4-8]
- No dosage adjustment required for the renally impaired
- Low sodium load
- Convenient, cost-effective q12h dosing

Contraindicated in patients with known allergy to the cephalosporin class of antibiotics

CEFOBID® 1g/2g q12h (cefoperazone sodium) IM/IV

A force against resistance

*Due to susceptible strains of indicated organisms, such as *P aeruginosa*

References **1.** Horan T, Culver D, Jarvis W, et al. Pathogens causing nosocomial infections: preliminary data from the National Nosocomial Infections Surveillance System. *Antimicrobic Newsletter* 1988;5(9):65-67. **2.** Data available on request from Roerig. **3.** Jenkins SG. Comparative susceptibility patterns of common clinical isolates to cefoperazone: 1981 to 1987. *Am J Med* 1988;85(suppl 1A):52-55. **4.** Mangi RJ, Greco T, Ryan J, Thorton G, Andriole VT. Cefoperazone versus combination antibiotic therapy of hospital acquired pneumonia. *Am J Med* 1988;84:68-74. **5.** Mangi RJ, Ryan J, Berenson C, et al. Cefoperazone versus ceftazidime monotherapy of nosocomial pneumonia. *Am J Med* 1988;85(suppl 1A):44-48. **6.** Mangi R, Peccerillo K, Moleski RJ. Treatment of nosocomial pneumonia. Presented as an educational exhibit at the 47th Annual Meeting of the American Society of Hospital Pharmacists, June 3-7, 1990, Boston, Mass. **7.** Cohen MS, Washton HE, Barranco SF. Multicenter clinical trial of cefoperazone sodium in the United States. *Am J Med* 1984;77:35-41. **8.** Kiehl A, Greenberg RN. Treatment of febrile neutropenic patients: evaluation of antibiotic regimens with or without vancomycin. Presented at the 24th Annual ASHP Midyear Clinical Meeting, December 3-7, 1989, Atlanta, Ga.

Brief Summary

CEFOBID® (cefoperazone sodium) *For Intravenous or Intramuscular Use*

CONTRAINDICATIONS: CEFOBID (cefoperazone sodium) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics. **WARNINGS**: BEFORE THERAPY WITH CEFOBID IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE THE USE OF SUBCUTANEOUS EPINEPHRINE AND OTHER EMERGENCY MEASURES.

PSEUDOMEMBRANOUS COLITIS HAS BEEN REPORTED WITH THE USE OF CEPHALOSPORINS (AND OTHER BROAD-SPECTRUM ANTIBIOTICS), THEREFORE, IT IS IMPORTANT TO CONSIDER ITS DIAGNOSIS IN PATIENTS WHO DEVELOP DIARRHEA IN ASSOCIATION WITH ANTIBIOTIC USE. **PRECAUTIONS**: Although transient elevations of the BUN and serum creatinine have been observed, CEFOBID alone does not appear to cause significant nephrotoxicity. However, concomitant administration of aminoglycosides and other cephalosporins has caused nephrotoxicity.

CEFOBID is extensively excreted in bile. The serum half-life of CEFOBID is increased 2-4 fold in patients with hepatic disease and/or biliary obstruction. In general, total daily dosage above 4 g should not be necessary in such patients. If higher dosages are used, serum concentrations should be monitored.

Because renal excretion is not the main route of elimination of CEFOBID, patients with renal failure require no adjustment in dosage when usual doses are administered. When high doses of CEFOBID are used, concentrations of drug in the serum should be monitored periodically. If evidence of accumulation exists, dosage should be decreased accordingly.

The half-life of CEFOBID is reduced slightly during hemodialysis. Thus, dosing should be scheduled to follow a dialysis period. In patients with both hepatic dysfunction and significant renal disease, CEFOBID dosage should not exceed 1-2 g daily without close monitoring of serum concentrations.

As with other antibiotics, vitamin K deficiency has occurred rarely in patients treated with CEFOBID. Those at risk include patients with a poor nutritional status, malabsorption states (e.g., cystic fibrosis), alcoholism, and patients on prolonged hyperalimentation regimens (administered either intravenously or via a nasogastric tube). Prothrombin time should be monitored in these patients and exogenous vitamin K administered as indicated.

A disulfiram-like reaction characterized by flushing, sweating, headache, and tachycardia has been reported when alcohol (beer, wine) was ingested within 72 hours after CEFOBID® (cefoperazone sodium) administration. Patients should be cautioned about the ingestion of alcoholic beverages following the administration of CEFOBID. A similar reaction has been reported with other cephalosporins.

Prolonged use of CEFOBID may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential.

CEFOBID should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. **Drug Laboratory Test Interactions**: A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution. **Carcinogenesis, Mutagenesis, Impairment of Fertility**: The maximum duration of CEFOBID animal toxicity studies is six months. In none of the *in vivo* or *in vitro* genetic toxicology studies did CEFOBID show any mutagenic potential at either the chromosomal or subchromosomal level. CEFOBID produced no impairment of fertility and had no effects on general reproductive performance or fetal development when administered subcutaneously at daily doses up to 500 to 1000 mg/kg prior to and during mating, and to pregnant female rats during gestation. These doses are 10 to 20 times the estimated usual single clinical dose. Cefoperazone had adverse effects on the testes of prepubertal rats at all doses tested. Subcutaneous administration of 1000 mg/kg per day (approximately 16 times the average adult human dose) resulted in reduced germinal cell population and vacuolation of Sertoli cell cytoplasm. The severity of lesions was dose dependent in the 100 to 1000 mg/kg per day range, the low dose caused a minor decrease in spermatocytes. This effect has not been observed in adult rats. Histologically the lesions were reversible at all but the highest dosage levels. However, these studies did not evaluate subsequent development of reproductive function in the rats. The relationship of these findings to humans is unknown. **Usage in Pregnancy, Pregnancy Category B**: Reproduction studies have been performed in mice, rats, and monkeys at doses up to 10 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to CEFOBID. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Usage in Nursing Mothers**: Only low concentrations of CEFOBID are excreted in human milk. Although CEFOBID passes poorly into breast milk of nursing mothers, caution should be exercised when CEFOBID is administered to a nursing woman. **Pediatric Use**: Safety and effectiveness in children have not been established. For information concerning testicular changes in prepubertal rats see Carcinogenesis, Mutagenesis, Impairment of Fertility. **ADVERSE REACTIONS**: In clinical studies the following adverse effects were observed and were considered to be related to CEFOBID® (cefoperazone sodium) therapy or uncertain etiology. **Hypersensitivity**: As with all cephalosporins, hypersensitivity manifested by skin reactions (1 patient in 45), drug fever (1 in 260), or a change in Coombs' test (1 in 60) has been reported. These reactions are more likely to occur in patients with a history of allergies, particularly to penicillin. **Hematology**: As with other beta-lactam antibiotics, reversible neutropenia may occur with prolonged administration. Slight decreases in neutrophil count (1 patient in 50) have been reported. Decreased hemoglobins (1 in 20) or hematocrits (1 in 20) have been reported, which is consistent with published literature on other cephalosporins. Transient eosinophilia has occurred in 1 patient in 10. **Hepatic**: Of 1285 patients treated with cefoperazone in clinical trials one patient with a history of liver disease developed significantly elevated liver function enzymes during CEFOBID therapy. Clinical signs and symptoms of nonspecific hepatitis accompanied these increases. After CEFOBID therapy was discontinued, the patient's enzymes returned to pretreatment levels and the symptomatology resolved. As with other antibiotics that achieve high bile levels, mild transient elevations of liver function enzymes have been observed in 5-10% of the patients receiving CEFOBID therapy. The relevance of these findings, which were not accompanied by overt signs or symptoms of hepatic dysfunction, has not been established. **Gastrointestinal**: Diarrhea or loose stools has been reported in 1 in 30 patients. Most of these experiences have been mild or moderate in severity and self-limiting in nature. In all cases, these symptoms responded to symptomatic therapy or ceased when cefoperazone therapy was stopped. Nausea and vomiting have been reported rarely.

Symptoms of pseudomembranous colitis can appear during or for several weeks subsequent to antibiotic therapy (see WARNINGS). **Renal Function Tests**: Transient elevations of the BUN (1 in 16) and serum creatinine (1 in 48) have been noted. **Local Reactions**: CEFOBID is well tolerated following intramuscular administration. Occasionally, transient pain (1 in 140) may follow administration by this route. When CEFOBID is administered by intravenous infusion some patients may develop phlebitis (1 in 120) at the infusion site.

Pfizer Roerig

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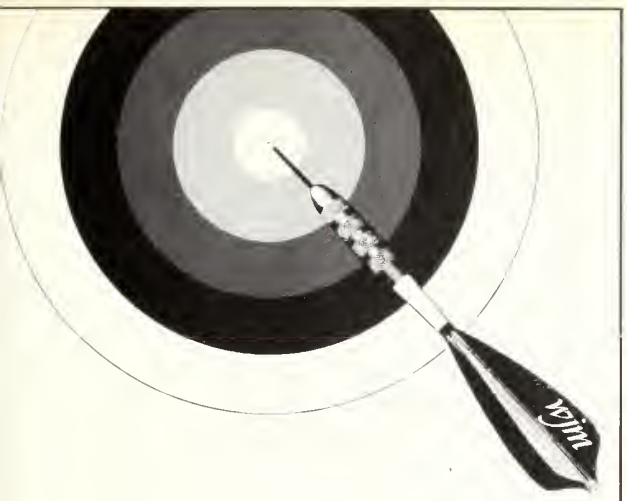

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Description: Yohimbine is a 3a-15a-20B-17a-hydroxy Yohimbine-16a-carboxylic acid methyl ester. The alkaloid is found in Rubaceae and related trees. Also in Rauwolfia Serpentina (L) Benth. Yohimbine is an indolalkylamine alkaloid with chemical similarity to reserpine. It is a crystalline powder, odorless. Each compressed tablet contains (1/12 gr.) 5.4 mg of Yohimbine Hydrochloride.

Action: Yohimbine blocks presynaptic alpha-2 adrenergic receptors. Its action on peripheral blood vessels resembles that of reserpine, though it is weaker and of short duration. Yohimbine's peripheral autonomic nervous system effect is to increase parasympathetic (cholinergic) and decrease sympathetic (adrenergic) activity. It is to be noted that in male sexual performance, erection is linked to cholinergic activity and to alpha-2 adrenergic blockade which may theoretically result in increased penile inflow, decreased penile outflow or both.

Yohimbine exerts a stimulating action on the mood and may increase anxiety. Such actions have not been adequately studied or related to dosage although they appear to require high doses of the drug. Yohimbine has a mild anti-diuretic action, probably via stimulation of hypothalmic centers and release of posterior pituitary hormone.

Reportedly, Yohimbine exerts no significant influence on cardiac stimulation and other effects mediated by B-adrenergic receptors, its effect on blood pressure, if any, would be to lower it; however no adequate studies are at hand to quantitate this effect in terms of Yohimbine dosage.

Indications: Yocon® is indicated as a sympathicolytic and mydriatric. It may have activity as an aphrodisiac.

Contraindications: Renal diseases, and patient's sensitive to the drug. In view of the limited and inadequate information at hand, no precise tabulation can be offered of additional contraindications.

Warning: Generally, this drug is not proposed for use in females and certainly must not be used during pregnancy. Neither is this drug proposed for use in pediatric, geriatric or cardio-renal patients with gastric or duodenal ulcer history. Nor should it be used in conjunction with mood-modifying drugs such as antidepressants, or in psychiatric patients in general.

Adverse Reactions: Yohimbine readily penetrates the (CNS) and produces a complex pattern of responses in lower doses than required to produce peripheral a-adrenergic blockade. These include, anti-diuresis, a general picture of central excitation including elevation of blood pressure and heart rate, increased motor activity, irritability and tremor. Sweating, nausea and vomiting are common after parenteral administration of the drug.[1,2] Also dizziness, headache, skin flushing reported when used orally.[1,3]

Dosage and Administration: Experimental dosage reported in treatment of erectile impotence.[1,3,4] 1 tablet (5.4 mg) 3 times a day, to adult males taken orally. Occasional side effects reported with this dosage are nausea, dizziness or nervousness. In the event of side effects dosage to be reduced to ½ tablet 3 times a day, followed by gradual increases to 1 tablet 3 times a day. Reported therapy not more than 10 weeks.[3]

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References:

1. A. Morales et al., New England Journal of Medicine 1221. November 12, 1981.
2. Goodman, Gilman — The Pharmacological basis of Therapeutics 6th ed., p. 176-188. McMillan December Rev. 1/85.
3. Weekly Urological Clinical Letter, 27:2, July 4, 1983.
4. A. Morales et al., The Journal of Urology 128: 45-47, 1982.

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(Continued from Page 570)

August 3-7—**Impulse Control Disorders and Addictions: Update and Review.** Southern California Neuropsychiatric Institute at Mauna Kea Beach Hotel, The Big Island, Hawaii. Tues-Sat. 24 hrs. Contact: Ann McCormick, 6794 La Jolla Blvd, La Jolla 92037. (619) 454-2102.

RADIOLOGY

June 1993—**Fellowship in Interventional Radiology for Radiologists.** UCSD at Medical Center. Weekly. 40 hrs. $700. Contact: UCSD.

August 12-15—**Physics of Diagnostic Radiology, Nuclear Medicine, and Radiation Biology.** UCSD on Campus. Thurs-Sun. Contact: UCSD.

October 18-20—**Radiology for the Non-Radiologists.** UCSD at Hyatt Regency, San Diego. Mon-Wed. 20 hrs. $450. Contact: Jacqueline Shiller, PO Box 84296, San Diego 92138. (619) 223-2997.

October 23-24—**MRI of the Musculoskeletal System.** UCSD at Hotel del Coronado, San Diego. Sat-Sun. 9 hrs. $275. Contact: UCSD.

October 25-29—**18th Annual San Diego Postgraduate Radiology Course.** UCSD at Hotel del Coronado, San Diego. Mon-Fri. 25 hrs. $595. Contact: UCSD.

October 29-31—**Annual Interventional Radiology Course.** UCSD at Hotel del Coronado, San Diego. Fri-Sun. 16 hrs. $375. Contact: UCSD.

November 12-14—**Advanced Seminars in Diagnostic Imaging.** UCSD at Ritz-Carlton, Laguna Niguel. Fri-Sun. 20 hrs. $500. Contact: UCSD.

RISK MANAGEMENT

July 19-20—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP Emergency Medical Group at San Diego. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, Risk Management Programs, (800) 451-7475.

September 27-28—**High Risk Emergency Medicine: Preventing Malpractice.** CAL/ACEP at Las Vegas, Nevada. Mon-Tues. 15 hrs. $345-$495. Contact: Kathy Hester, (800) 451-7475.

SURGERY

August 11-14—**7th International Symposium on the Latest Advances in Cosmetic Surgery of the Face.** Foundation for Facial Plastic Surgery at Hyatt Newporter Resort, Newport Beach. Wed-Sat. 25 hrs. $795. Contact: Angela O'Mara, (714) 759-7678.

VASCULAR DISEASE

June 25-26—**Advances in Vascular Disease.** Medical Educational Resources at Disneyland Hotel, Anaheim. Fri-Sat. 11 hrs. Contact: MER, 1500 W Canal Ct, Ste 500, Littleton, CO 80120-4528. (800) 421-3756.

GENERAL/MULTIDISCIPLINARY

June 25—**Bioethics Conference.** UCD at Hyatt Regency, Sacramento. Fri. Contact: UCD.

October 14-17—**Women in Medicine.** UCSD at San Diego Hilton. Thurs-Sun. 15 hrs. $300. Contact: UCSD.

HOME STUDY/SELF ASSESSMENT

Audio-Digest Foundation. California Medical Association. Contact: Audio-Digest Foundation, 1577 E Chevy Chase, Glendale 91206. (213) 245-8505.

COLORADO

This listing of continuing medical education programs in Colorado is compiled by the Denver Medical Society. To list CME programs here, please send information at least two months in advance to: Mr Robert L. Kennedy, Denver Medical Society, 1850 Williams Street, Denver, CO 80218; or telephone (303) 377-1850.

Brochures, course information, and registration forms are available from the contact person or organization.

June 13-19—**39th Annual Family Practice Review.** U of Colo at YMCA of The Rockies, Estes Park. Sun-Sat. Contact: Phyllis Schroeder, U of Colo.

June 14-16—**Community Health Traineeship Program.** Children's Hospital, Denver. Mon-Wed. Contact: Outreach Office. (303) 861-6668.

July 2-9—**Molecular Biology in Clinical Oncology: A Workshop.** U of Colo at Given Institute, Aspen. Fri-Fri. Contact: U of Colo.

July 13—**Cultural Considerations in Perinatal Nursing.** Children's Hospital at University Hospital, Denver. Tues. Contact: Trish Beachy, (303) 270-8376.

July 18-23—**29th Annual Internal Medicine Program.** U of Colo at Estes Park. Sun-Fri. Contact: U of Colo.

July 26-30—**Breast Imaging and Intervention.** U of Colo at Colorado Springs. Mon-Fri. Contact: U of Colo.

July 26-30—**20th Annual Renal Disease Program.** U of Colo at Given Institute, Aspen. Mon-Fri. Contact: U of Colo.

July 30-August 1—**2nd Annual Medical Ethics Conference.** U of Colo at Aspen. Fri-Sun. Contact: Phyllis Schroeder, U of Colo.

August 2-6—**17th Annual Dynamic Psychotherapy Program.** U of Colo at Given Institute, Aspen. Mon-Fri. Contact: Phyllis Schroeder, U of Colo.

August 8-12—**36th Annual Pediatric Program.** U of Colo at Given Institute, Aspen. Sun-Thurs. Contact: U of Colo.

August 13-15—**Diagnosis and Management of Perinatal Arrhythmias.** U of Colo at Given Institute, Aspen. Fri-Sun. Contact: Phyllis Schroeder, U of Colo.

August 16-17—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver. Mon-Tues. Contact: Outreach Office, (303) 861-6188.

August 16-19—**Respiratory Therapy Traineeship Program.** Children's Hospital, Denver. Mon-Thurs. Contact: Jeff Griebel, (303) 861-6668.

August 19-21—**3rd Annual Musculoskeletal Infection Society Meeting.** U of Colo at Snowmass Village. Thurs-Sat. Contact: U of Colo.

August 23-28—**18th Annual Primary Musculoskeletal Care Program.** U of Colo at The Village, Breckenridge. Mon-Sat. Contact: Phyllis Schroeder, U of Colo.

September 20-21—**Pediatric Nursing Traineeship Program.** Children's Hospital, Denver, Mon-Tues. Contact: Outreach Office, (303) 861-6668.

September 21-22, 28-29—**Comprehensive Perinatal Nursing Course.** Children's Hospital at University Hospital, Denver. Tues-Wed. Contact: Trish Beachy, (303) 270-8376.

September 23-25—**The Penrose Cancer Conference: Neoplastic Diseases of the Breast and Ovary.** The Penrose-St Francis Healthcare System at the Broadmoor Hotel, Colorado Springs. Thurs-Sat. Contact: Deborah Hood, Penrose-St Francis Health Care System, PO Box 7021, Colorado Springs 80933-9939. (719) 630-5716.

October 14-16—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie, Wyoming. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010.

November 11-13—**Rural Perinatal Traineeship Program.** Children's Hospital, Denver. Thurs-Sat. Contact: Outreach Office, (303) 861-6668.

First Wednesday of Each Month—**Various Topics in Neurology.** Sponsored by the Colorado Society of Clinical Neurologists. Contact: Colorado Society of Neurologists, (303) 449-3566.

CONTACT INFORMATION

U of Colo—Contact: University of Colorado School of Medicine, Office of Continuing Medical Education, 4200 E 9th Ave, Denver, CO. (303) 270-5195 or (800) 882-9153; FAX (303) 270-6761.

IDAHO

July 28-31—**Imaging on Lake Coeur d'Alene—A Summer Radiology Meeting on One of the Five Most Beautiful Lakes in the World!** Coeur d'Alene Resort, Coeur d'Alene. Wed-Sat. Contact: Kathy Fischer, Sacred Heart Medical Center, Department of Radiology, PO Box 2555, Spokane, WA 99220-2555 (509) 455-3352.

July 29-31—**Idaho Medical Association Annual Meeting.** Sun Valley. Thurs-Sat. Contact: IMA, 305 W Jefferson, PO Box 2668, Boise 83701. (208) 344-7888.

(Continued on Page 654)

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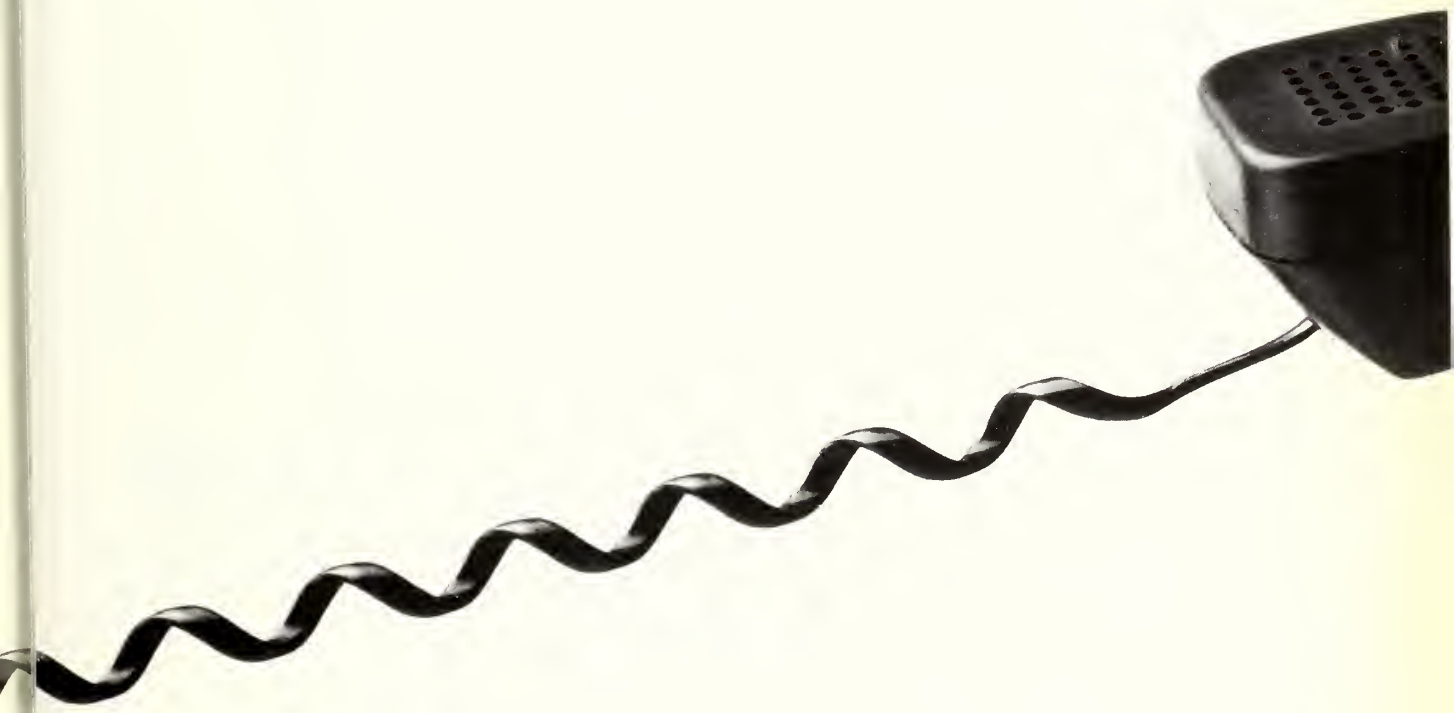

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REBECCA S. BAHN, MD
Dr Bahn is Consultant, Division of Endocrinology, Mayo Clinic/Foundation, Rochester, Minnesota.

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DONALD P. TASHKIN, MD
Dr Tashkin is Professor of Medicine, Division of Pulmonary and Critical Care Medicine, University of California, Los Angeles, School of Medicine.

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In Memoriam

California Medical Association

ABATECOLA, PHILIP M., Banning. Died Jan 30, 1993, aged 42. Graduate of St Louis University School of Medicine, St Louis, Missouri, 1976. Licensed in California in 1977. Dr Abatecola was a member of the Riverside County Medical Association.

BEMRICK, ROBERT J., Sacramento. Died Jun 2, 1992, aged 62. Graduate of University of Wisconsin Medical School, Madison, 1956. Licensed in California in 1959. Dr Bemrick was a member of the Sacramento-El Dorado Medical Society.

BLEIBERG, DONALD J., Palo Alto. Died Apr 4, 1993, aged 78. Graduate of University of Southern California, Los Angeles, 1941. Licensed in California in 1941. Dr Bleiberg was a member of the Santa Clara County Medical Association.

CASTRO, MAURICIO V., Redwood City. Died Apr 1993, aged 65. Graduate of Facultad De Med Univ Nacional E'El Salva, San Salvador, 1963. Licensed in California in 1966. Dr Castro was a member of the San Mateo County Medical Society.

DICKSON, LOUIS L., Chula Vista. Died Mar 1993, aged 79. Graduate of Loma Linda University, Loma Linda, California, 1945. Licensed in California in 1946. Dr Dickson was a member of the San Diego County Medical Society.

HARAVEY, FRANCOIS, Laguna Niguel. Died Mar 8, 1993, aged 59. Graduate of Tulane University School of Medicine, New Orleans, Louisiana, 1962. Licensed in California in 1966. Dr Haravey was a member of the Orange County Medical Association.

HERMOSILLO, ELIAS G., Stockton. Died Mar 31, 1993, aged 79. Graduate of Fac Med Univ Nacional Autonoma De Mexico, Mexico, 1939. Licensed in California in 1941. Dr Hermosillo was a member of the San Joaquin County Medical Society.

LUNDE, FINN, Roseville. Died Mar 9, 1993, aged 65. Graduate of Medisinske Fakultet Universitetet I Oslo, Oslo, Norway, 1952. Licensed in California in 1964. Dr Lunde was a member of the Placer-Nevada County Medical Society.

MOORE, JACK D., Oakland. Died Nov 21, 1992, aged 78. Graduate of Temple University School of Medicine, Philadelphia, Pennsylvania, 1940. Licensed in California in 1947. Dr Moore was a member of the Alameda-Contra Costa Medical Association.

NILSSON, JOHN M., Sacramento. Died Oct 30, 1992, aged 70. Graduate of Harvard Medical School, Boston, Massachusetts, 1945. Licensed in California in 1948. Dr Nilsson was a member of the Sacramento-El Dorado Medical Society.

PACE, CLINTON A., Roseville. Died Mar 7, 1993, aged 63. Graduate of University of Illinois College of Medicine, Chicago, 1955. Licensed in California in 1959. Dr Pace was a member of the Placer-Nevada County Medical Society.

PAYTON, ROBERT C., Beaumont. Died Jan 8, 1993, aged 72. Graduate of University of Iowa College of Medicine, Iowa City, 1950. Licensed in California in 1951. Dr Payton was a member of the Riverside County Medical Association.

SCHIELE, DANIEL R., Mission Viejo. Died Mar 13, 1993, aged 52. Graduate of University of Missouri School of Medicine, Columbia, 1974. Licensed in California in 1975. Dr Schiele was a member of the Orange County Medical Association.

SOTO-HALL, RALPH, San Francisco. Died Feb 3, 1993, aged 94. Graduate of University of California, San Francisco, School of Medicine, 1923. Licensed in California in 1923. Dr Soto-Hall was a member of the San Francisco Medical Society.

SPENCE, CLARENCE H., Santa Ana. Died Feb 1993, aged 59. Graduate of Howard University School of Medicine, Washington, DC, 1966. Licensed in California in 1968. Dr Spence was a member of the Orange County Medical Association.

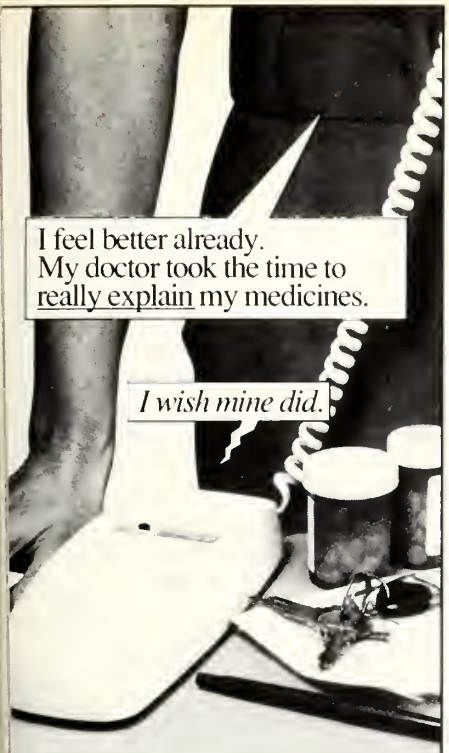
STANKE, JIRINA, Loma Linda. Died Feb 20, 1993, aged 44. Graduate of Pritzker School of Medicine, University of Chicago, Chicago, Illinois, 1977. Licensed in California in 1979. Dr Stanek was a member of the San Bernardino County Medical Society.

STINSON, RALF H., San Mateo. Died Mar 4, 1993, aged 73. Graduate of Stanford University School of Medicine, Stanford, California, 1951. Licensed in California in 1954. Dr Stinson was a member of the San Mateo County Medical Society.

VONSALTZA, JOHN W. H., San Jose. Died Feb 9, 1993, aged 80. Graduate of Stanford University School of Medicine, Stanford, California, 1939. Licensed in California in 1941. Dr Vonsaltza was a member of the Santa Clara County Medical Association.

WEDELL, JOSEPH W., Redwood City. Died Mar 6, 1993, aged 69. Graduate of University of Utah College of Medicine, Salt Lake City, 1950. Licensed in California in 1951. Dr Wedell was a member of the San Mateo County Medical Society.

WHEELER, JERRY RONALD, Arcata. Died Jan 31, 1993, aged 50. Graduate of University of Kentucky College of Medicine, Lexington, 1968. Licensed in California in 1969. Dr Wheeler was a member of the Humboldt-Del Norte Medical Society.



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AUGMENTIN®

amoxicillin/clavulanate potassium

See complete prescribing information in SmithKline Beecham Pharmaceuticals literature or *PDR*. The following is a brief summary.

Indications and Usage: *Augmentin* is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below:

Lower Respiratory Tract Infections caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Otitis Media caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Sinusitis caused by β-lactamase-producing strains of *Hemophilus influenzae* and *Moraxella (Branhamella) catarrhalis*

Skin and Skin Structure Infections caused by β-lactamase-producing strains of *Staphylococcus aureus*, *E. coli*, and *Klebsiella* spp.

Urinary Tract Infections caused by β-lactamase-producing strains of *E. coli*, *Klebsiella* spp. and *Enterobacter* spp.

While *Augmentin* is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to *Augmentin* treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and β-lactamase-producing organisms susceptible to *Augmentin* should not require the addition of another antibiotic.

Bacteriological studies, to determine the causative organisms and their susceptibility to *Augmentin*, should be performed together with any indicated surgical procedures.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to *Augmentin* when there is reason to believe the infection may involve any of the β-lactamase-producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

Contraindications: A history of allergic reactions to any penicillin is a contraindication.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS HAVE BEEN REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH ANAPHYLAXIS IS MORE FREQUENT FOLLOWING PARENTERAL THERAPY, IT HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. THESE REACTIONS ARE MORE LIKELY TO OCCUR IN INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY AND/OR A HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. THERE HAVE BEEN REPORTS OF INDIVIDUALS WITH A HISTORY OF PENICILLIN HYPERSENSITIVITY WHO HAVE EXPERIENCED SEVERE REACTIONS WHEN TREATED WITH CEPHALOSPORINS. BEFORE INITIATING THERAPY WITH ANY PENICILLIN, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF AN ALLERGIC REACTION OCCURS, *AUGMENTIN* SHOULD BE DISCONTINUED AND THE APPROPRIATE THERAPY INSTITUTED. **SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including *Augmentin*, and has ranged in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is 1 primary cause of "antibiotic associated colitis."

Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation and treatment with an antibacterial drug clinically effective against *C. difficile* colitis.

Precautions: General: While *Augmentin* possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.

A high percentage of patients with mononucleosis who received ampicillin develop a skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.

The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

Drug Interactions: Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with *Augmentin* may result in increased and prolonged blood levels of amoxicillin.

The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with *Augmentin* and allopurinol administered concurrently.

Augmentin should not be co-administered with Antabuse® (disulfiram).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

Pregnancy (Category B): Reproduction studies have been performed in mice and rats at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to *Augmentin*. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery: Oral ampicillin class antibiotics are generally poorly absorbed during labor. Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions and duration of contractions. However, it is not known whether the use of *Augmentin* in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Ampicillin class antibiotics are excreted in the milk, therefore, caution should be exercised when *Augmentin* is administered to a nursing woman.

Adverse Reactions: *Augmentin* is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3% of patients discontinued therapy because of drug-related side effects. The most frequently reported adverse effects were diarrhea/loose stools (9%), nausea (3%), skin rashes and urticaria (3%), vomiting (1%) and vaginitis (1%).

The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include abdominal discomfort, flatulence and headache.

The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, enterocolitis and pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see WARNINGS).

Hypersensitivity reactions: Skin rashes, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis/arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson Syndrome), and an occasional case of exfoliative dermatitis have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin (see WARNINGS).

Liver: A moderate rise in AST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with *Augmentin*. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or after therapy. Complete resolution has occurred with time.

Hemic and Lymphatic Systems: Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with *Augmentin*.

Central Nervous System: Reversible hyperactivity, agitation, anxiety, insomnia, confusion, behavioral changes, and/or dizziness have been reported rarely.

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- Actively destroys ß-lactamase[4,5]

* For susceptible strains of indicated organisms. *Augmentin* is appropriate initial therapy when you suspect ß-lactamase-producing organisms.

† Latest available annual data: January to December 1991.

‡ *In vitro* susceptibility does not necessarily imply *in vivo* efficacy.

Please see brief summary of prescribing information for contraindications, warnings, precautions and adverse reactions on adjacent page.

References: 1. Neu HC, Wilson APR, Grüneberg RN: Amoxicillin/clavulanic acid — a review of its efficacy in over 38,500 patients from 1979 to 1992. *J Chemother* 1993. In press. **2.** Data on file, SmithKline Beecham Pharmaceuticals. **3.** Data from the Institutes for Microbiology Research, Franklin, Tenn. **4.** Brown R, Pinkerton R, Tuttle M. Respiratory infections in smokers. *Am Fam Physician* 1987;36:133-140. **5.** Neu HC: Contribution of beta-lactamases to bacterial resistance and mechanisms to inhibit beta-lactamases. *Am J Med* 1985;79(suppl 5B):2-12.

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Philadelphia, PA 19101

Conferences and Reviews

Hansen's Disease

Discussant
ROBERT H. GELBER, MD

This discussion was selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from a transcription, it has been edited by Nathan M. Bass, MD, PhD, Associate Professor of Medicine, under the direction of Lloyd H. Smith Jr, MD, Professor of Medicine and Associate Dean in the School of Medicine.

HOMER BOUSHEY, MD*: *The topic of this conference—Hansen's disease—will be discussed by Robert Gelber, MD. Dr Gelber has been active in the study of the interplay between the infecting organism, the immune responsiveness of the host, and the action of pharmacologic agents in modifying Hansen's disease. On the basis of knowledge obtained from his work, he is able to project how modern advances in pharmacology, in antibiotics, and perhaps in the development of vaccines will change the expression of this important disease in the next decade.*

Hansen's Disease and Social Stigma

ROBERT H. GELBER, MD†: In 1873, a Norwegian physician, Gerhard Henrik Armauer Hansen, discovered that a bacterium, *Mycobacterium leprae,* was the cause of an age-old disease, leprosy. To that time, a relationship between a specific bacterium and a human disease had been established only for anthrax. Today we call leprosy "Hansen's disease," not so much to honor Hansen's discovery but because the words "leprosy" and "leper" have such negative connotations; it is hoped that this more neutral name may help in the difficult task of reducing the social stigma from which patients still suffer enormously. The horror of leprosy largely results from the fact that *M leprae* is the only bacterium that invades peripheral nerves, resulting in neuropathy that in turn results in myopathy and insensitivity—particularly to pain, temperature, and fine touch. This insensitivity allows for trauma, secondary infection, deformity, and at times amputation of the distal extremities. In the Bible "lepers" were judged "unclean" and placed "outside the camp." Yet, it is noteworthy that biblical "leprosy" was not leprosy itself but probably certain other disfiguring dermatologic diseases. Leprosy originated in China or India and did not arrive in the Middle East until long after the biblical era. Nevertheless, in western society, this diagnosis continues to carry a social stigma. Also, in Asian societies, patients with leprosy are often ostracized; in traditional Chinese families, those discovered to have the disease are often told to "never darken the door again."

With early diagnosis and modern therapy, the severe neurologic sequelae of leprosy can fortunately now be largely prevented, and patients are now more likely to suffer from the psychosocial aspects of their disease than from the actual medical effects. In the lay press, patients with the acquired immunodeficiency syndrome (AIDS) have been referred to as "the new lepers" and as irrationally ostracized as have been Hansen's disease sufferers for centuries.

To emphasize the importance of the leprosy stigma to affected persons, I shall share an anecdote. One morning I came in to the hospital to see patients on rounds. The previous evening, the house staff had evaluated a young man from the Philippines with the initial diagnosis of lepromatous leprosy. As I came in the door I was greeted by, "Oh, Dr Gelber, I guess you are the one who knows about this. Am I really one of the living dead?" I was startled by this question, not knowing where the idea came from, and eventually found out that in Europe in the Middle Ages, when people were diagnosed with the illness, they were declared by the church as legally dead and all their material goods were distributed. Because much of the culture of the Philippines emanated from Spain, that idea has stuck. Furthermore, before the introduction of antibiotics in the Philippines, the control of leprosy involved the removal of patients from their homes to institutions (leprosaria) and even the removal of babies at birth from affected parents. Even in these more enlightened times, when patients with leprosy are no longer put in institutions, many patients in the Philippines will hide their illness, getting progressively more deformed, rather than face the psychosocial consequences of their diagnosis and the social ostracism that attends it.

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ABBREVIATIONS USED IN TEXT

AFB = acid-fast bacilli
AIDS = acquired immunodeficiency syndrome
WHO = World Health Organization

Epidemiology

Leprosy is far from a disease of the past. It is estimated by the World Health Organization (WHO) that there are more cases worldwide today than ever before in history—perhaps as many as 5.5 million.[1] The disease prevalence is highest in Africa, although most of the world's cases are found in Asia. In India, which has the most disease, it is estimated that almost 1% of the population—about 3 million people—have leprosy. The disease is also endemic in many other developing countries, particularly in Latin America, especially in the Amazon Basin of Brazil, and the Pacific.*

Although it is estimated that there are only about 6,000 cases of leprosy in the United States, the disease is on the rise in this country owing to the fact that current migration to the United States is largely from the endemic developing countries, including Latin America and Asia. In 1960 only 60 cases were reported to the Centers for Disease Control and Prevention annually; this has risen to about 150 cases to 200 cases annually. A few endemic cases occur in the United States, but these are confined to the states of Hawaii, Louisiana, and Texas. In the United States, leprosy is largely found on the West Coast (particularly California), Hawaii, and Texas. This geographic distribution reflects the preferred areas of settlement for immigrants from the Philippines, Mexico, and Southeast Asia. I treat about 650 leprosy patients here in northern California, at one of the four West Coast US Public Health Service-sponsored clinics. The other three clinics are in Los Angeles, San Diego, and Seattle. These four clinics see about 60% of the leprosy patients under treatment in the United States.

As with the major American systemic fungal diseases in their disseminated forms, lepromatous leprosy shows a considerable male-to-female predominance, being about twice as prevalent in men. Coccidioidomycosis in its disseminated form is about three times more common, disseminated histoplasmosis about four to five times more common, and systemic blastomycosis as much as six to seven times more common in men than in women.

These systemic fungal diseases share with *M leprae* infection intracellular parasitism, the protective arm of immunity for which is cell-mediated immunity. It is a well-recognized but poorly understood phenomenon that, whether it be in humans or in mice, females have enhanced immune function. This of course predisposes women to a greater prevalence of immune-mediated diseases, like lupus erythematosus and rheumatoid arthritis, but may also be protective in the case of diseases such as lepromatous leprosy. Indeed, immunologists who work with cellular immune function in mice generally choose female mice because they have more regular and profound cellular immune responses.

If there is a simple point worth emphasizing, it is that people with skin rashes and evidence of peripheral neuropathy who originate from leprosy endemic countries may indeed have leprosy. I point this out because the preceding director of Hansen's Disease Research Laboratories, Paul Fasal, MD, who retired in 1979, used to say that the mean time from medical presentation to diagnosis in California was two years. At that time Hansen's disease in California was certainly more of a rarity than it is today. Although such a delay in diagnosis is seldom seen today, it is still not unusual for patients to see several physicians and be given dermatologic preparations and at times antibiotics for a considerable period before the diagnosis is made. Thus I urge that for patients who present with peculiar rashes or signs of peripheral nerve dysfunction and who hail from endemic countries, Hansen's disease be included in the differential diagnosis.

Incubation Period

The incubation period for leprosy is uniquely long among the bacterial diseases, with a minimum of 2 to 3 years, probably an average of 5 to 7 years, and a maximum of 40 to 50 years. I know of several Filipino men in the sixth or seventh decade of life who permanently left the Philippines just after World War II and who are just now having signs and symptoms of the disease. The long incubation period is a function of two factors:

- *Mycobacterium leprae* is a slowly growing organism. As is well known, *Escherichia coli* divides in culture every 20 minutes and *Mycobacterium tuberculosis* about once a day. *M leprae* does not grow in artificial media nor—at least convincingly—in tissue culture, but in the feet of mice it divides every two weeks[2]—a very slow rate of growth indeed.
- The other factor contributing to the long incubation period of leprosy is that, among the human bacterial diseases, lepromatous leprosy accumulates by many orders of magnitude the greatest number of bacteria before a patient has signs and symptoms of disease. In these patients, though *M leprae* invades every organ system except the lungs and central nervous system, it is found preferentially in the skin, dermal nerves, and larger peripheral nerve trunks.

The skin of patients with lepromatous leprosy may contain as many as 10^9 bacilli per gram, which may result in bacilli accounting for 15% of the skin's dry weight. In untreated patients with lepromatous leprosy, there is a constant afebrile bacteremia of 10^5 bacilli per milliliter of blood.[3] To put this number in some perspective, in gram-negative sepsis or streptococcal endocarditis, it would be rare to have more than 10^3 bacteria per milliliter of blood.

Transmission

It is surprising that there is still uncertainty about how leprosy is transmitted. The commonest view was that it

*See also the editorial by R. A. Miller, MD, "Hansen's Disease—A Time for Cautious Optimism," on pages 631-633 of this issue.

was spread by skin-to-skin contact. Yet, if the skin of patients heavily infected with lepromatous leprosy is examined histologically, there are no organisms in the epidermis or the most superficial levels of the dermis. There may be situations where, because of either anesthesia and consequent trauma or lepra reactions with ulceration, the epidermis gets denuded, allowing a direct egress of the organisms from the skin. Skin-to-skin contact, however, is not currently considered a common route of disease transmission.

The most widely held view of transmission is that it occurs by nasal droplet infection, and the evidence for this is somewhat convincing. Immunosuppressed rodents placed in an aerosol of *M leprae* become diseased,[4] and the number of organisms in a sneeze from a patient with untreated lepromatous leprosy is about the same as that in a cough from a patient with untreated cavitary pulmonary tuberculosis.[5]

Other possible means of transmission may also be important, and the one that is most attractive, although it is essentially unproved, is that of direct dermal inoculation. Such an alternative hypothesis seems necessary to explain the epidemiology of leprosy in India. Tuberculosis in India, as might be expected of a pathogen spread by the respiratory route, is an urban disease. On the other hand, leprosy in India is largely a rural disease[6] and is especially prevalent in persons whose occupations bring them in close contact with the soil. Furthermore, *M leprae* can be found in the soil,[7,8] people in endemic countries often do not wear shoes, and direct dermal inoculation may result in leprosy transmission. There was an infamous tattoo parlor in Hong Kong where a few sailors who were tattooed came down with the disease[9]; clearly the tattoo needles were not being properly sterilized. Also, one of my colleagues, when attempting to inoculate a mouse footpad with *M leprae,* missed the mouse, hitting his finger. A couple of months later there was a nodule at the site of the needle stick that when a biopsy was taken showed granulomas and acid-fast bacilli. Thus, there are reasons to think that direct dermal inoculation may also be a route of leprosy transmission.

In terms of alternative routes of disease transmission, bed bugs and mosquitos in the vicinity of leprosaria regularly harbor *M leprae,*[10] and mosquitos, after biting patients with lepromatous leprosy, are able to transmit *M leprae* to mice as long as 48 hours later.[11] When I worked at the National Institute for Medical Research in London, we conducted an experiment with *Mycobacterium lepraemurium,* which causes a mouse mycobacterial disease that results in a high level of bacteremia (10^7 bacilli per milliliter of blood). In this study, we infected mice with *M lepraemurium* and had mosquitos bite these mice. Later, the mosquitos were allowed to feed on uninfected mice; by these means, we were able to transmit this mycobacterial disease for as long as five days after the original blood meal.

It is still uncertain how the organism is spread, and there are grounds for there being several routes of disease propagation. It could be that the spectrum of the disease is not entirely a function of precedent cellular immune responses but has more to do with the inoculum size and route of infection. One of the reasons I have remained intrigued by the pathobiology of leprosy is that, despite the fact that this disease is of such historical interest, there are still such basic questions concerning its pathogenesis yet to be elucidated.

Whatever the mode of *M leprae* transmission, it is a disease that tends to reside within households. If a person in an endemic country contracts lepromatous leprosy, the chance that another person in the household will get it is about 10%. In nonendemic countries, including the United States and Holland, for reasons that remain obscure, the disease develops in household contacts of lepromatous leprosy only 1% of the time. Patients with tuberculoid leprosy, on the other hand, do not appear to be a source of disease transmission, even to persons in their immediate household.

Clinical Presentation and Disease Spectrum

Patients present with three principal manifestations: various skin rashes, consequences of the peripheral neuropathy, and chronic nasal congestion (only in the lepromatous form). The peripheral neuropathy may result in muscle weakness. The ulnar nerve is the nerve trunk most commonly involved, and this may lead to clawing of the fourth and fifth fingers and weakness and wasting of the dorsal interosseous musculature of the affected hand. If the peroneal nerve is involved, footdrop results. Hypoesthesia may result in chronic recurrent plantar ulceration, as well as burns and other trauma to the distal extremities that, when associated with secondary infection, may result in the loss of digits.

Leprosy is a disease with a distinct clinical pathologic spectrum (Table 1) associated with a range of host immunologic reactivity. At one polar extreme of the spectrum is tuberculoid leprosy, which is manifested by one or more hypopigmented anesthetic macules with distinct, often erythematous, borders (Figure 1). In tuberculoid disease, pathologic and enlarged nerve trunks often occur spatially related to the skin lesions, are generally asymmetric, and may at times be the sole physical finding ("neural leprosy"). Patients with tuberculoid leprosy histologically have dermal granulomas consisting of leukocytes, epithelioid cells, and Langhans' giant cells, which are frequently associated with dermal appendages, particularly dermal nerves (Figure 2). At times the granuloma may invade and actually destroy dermal nerves, a process almost pathognomonic of leprosy and that distinguishes it from other dermal granulomatous processes, particularly sarcoidosis. On acid-fast stain, few or no acid-fast bacilli (AFB) are seen in the dermis of patients with tuberculoid disease, and tuberculoid patients' peripheral blood lymphocytes regularly recognize *M leprae* in vitro. The rim of a tuberculoid macule is the preferred biopsy site for diagnostic purposes, normal-appearing skin in these patients being histologically unremarkable.

On the other end of the spectrum, patients with lepromatous leprosy have infiltrated, nodular, and plaquelike

TABLE 1.—*Features of Polar Forms of Leprosy*

Clinical Feature	Polar Forms of Leprosy: Tuberculoid	Polar Forms of Leprosy: Lepromatous
Skin lesions	Hypopigmented, anesthetic macules with defined borders	Infiltrated nodules and plaques
Peripheral neuropathy	Early and asymmetric	Later and symmetric
Dermal histology	Granuloma with numerous lymphocytes, epithelioid cells, and foreign body giant cells: few or absent acid-fast bacilli	Highly vacuolated foamy macrophages; many acid-fast bacilli
Cell-mediated immunity to *Mycobacterium leprae*	Present	Absent
Antibodies to *M leprae*	Present about ⅔ of time	Almost invariably present
Serologic tests false-positive	No	Often

skin lesions (Figure 3). They may have loss of eyebrows and eyelashes, and their peripheral neuropathy and nerve enlargements are generally more symmetric. Skin biopsies preferably are taken from lesional areas, but normal-appearing skin will also be generally infected, the dermis showing many AFB, frequently in clusters, called globi (Figure 4), and numerous highly vacuolated fat-laden macrophages, called foam cells (Figure 5). Patients with lepromatous leprosy are anergic to *M leprae* but, unlike patients with lymphoma, carcinomatosis, or AIDS, mount normal immune responses to other antigens and have positive skin tests for purified protein derivative if concomitantly infected with *M tuberculosis* (Figure 6). Both T-cell and macrophage defects have been described in patients with lepromatous leprosy.[12-14] The *M leprae*-specific T-cell anergy in lepromatous leprosy may be either a function of an abundance of suppressor T cells or a result of "immune tolerance" from large amounts of *M leprae*-derived immunosuppressant lipids and carbohydrates.[15,16] Particular candidate molecules for this are the *M leprae*-specific phenolic glycolipid and lipoarabinomannan.[17-19]

Figure 1.—A hypopigmented macule of tuberculoid leprosy shows a defined border.

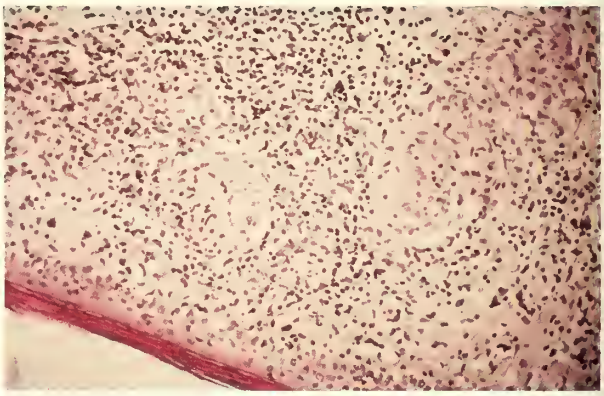

Figure 2.—The histologic appearance of the dermis in tuberculoid leprosy is shown (hematoxylin and eosin stain).

Patients in the middle of the spectrum, having features of both polar forms, are said to have borderline leprosy.

Antimicrobial Therapy

There are only four drugs commonly available to treat leprosy: dapsone, clofazimine, ethionamide, and rifampin, with only rifampin being bactericidal for *M leprae* in humans. Dapsone has the virtue of being inexpensive—$1 per year for the usual 100-mg-per-day adult daily dose—and relatively nontoxic. It causes hemolysis in all patients, which may result at times in anemia, especially in patients with glucose-6-phosphate dehydrogenase deficiency, and it may be allergenic. Clofazimine is generally administered to adults in a daily dose of 50 to 100 mg or 100 mg three times a week. Unfortunately, its use results in a red-black skin discoloration that is often uneven and frequently unacceptable to light-skinned persons. Also, taking clofazimine may result in various gastrointestinal side effects. Ethionamide, 250 to

Figure 3.—The infiltrated lesions of lepromatous leprosy are shown. Note the sparing of the midline of the back, the dermis therein being 5°C warmer than at the posterior axillary line. Other warm areas—scalp, axilla, and groin—are also generally spared in lepromatous leprosy.

500 mg daily in adults, may also cause gastrointestinal irritation and, more important, liver toxicity, especially when combined with rifampin; thus, its use cannot be recommended together with rifampin in areas of the world where liver function cannot be carefully monitored. Rifampin, which also may be hepatotoxic, is unfortunately expensive: approximately $1 for a usual adult 600-mg dose. For this reason, the WHO recommends it be administered but once a month, rather than, as is done in the United States, daily.

Regimens to treat leprosy are presented in Table 2. As can be seen, my recommendations differ from those of WHO. These differences stem from judgments concerning the prevalence of dapsone resistance and the significance of bacterial persistence. The WHO regards dapsone resistance to be of sufficient concern that its efficacy alone cannot be relied on.[20] I have found no primary dapsone resistance in the United States of any clinical importance, however.[21] The WHO considers that although viable *M leprae* can be obtained from the skin of treated patients after prolonged therapy,[22,23] the risk of these drug-sensitive "persisters" relapsing is minimal; I remain unconvinced of this. On these grounds, the WHO recommends three drugs for lepromatous disease and finite periods of therapy,[20] whereas I and other clinicians use only two drugs but with lifelong treatment.

Recently minocycline hydrochloride,[24,25] some of the newer macrolide antibiotics, particularly clarithromycin,[25-27] and a number of fluoroquinolones[28,29] have been found to be bactericidal against *M leprae* in mice. Minocycline and two of the fluoroquinolones, pefloxacin and ofloxacin, have been found to be more rapidly effective than either dapsone or clofazimine in clinical trials.[30,31] Thus there are prospects that new antimicrobials may emerge to further improve the therapy for leprosy.

Slit-skin smears are a useful means of determining disease severity and the efficacy of treatment. Skin smears are obtained by scraping the dermis with a scalpel or razor blade and are examined microscopically both for the density of organisms (bacteriologic index) and the percentage of organisms that stain evenly (morphologic index).

Generally smears are taken from six different skin sites, traditionally the earlobes, anterior knees, and posterior elbows—sites that can be cleared of blood by pinching—but other lesional areas may be substituted. Patients with lepromatous leprosy generally have an initial bacteriologic index of 4+ to 6+, which falls by 1+ per year of effective therapy, becoming zero generally at about five years. The fall of the morphologic index corresponds with

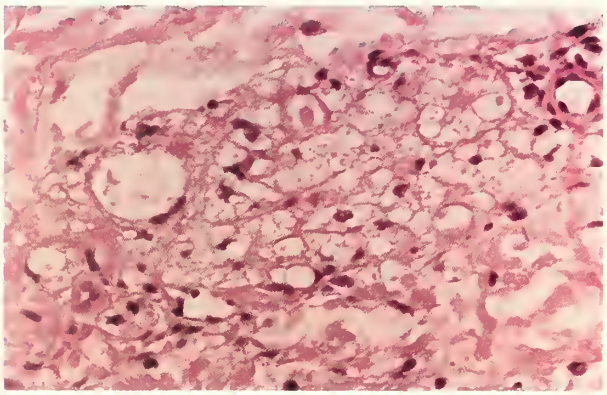

Figure 4.—An acid-fast stain of the dermis in untreated lepromatous leprosy shows the numerous clustered bacilli, or globi.

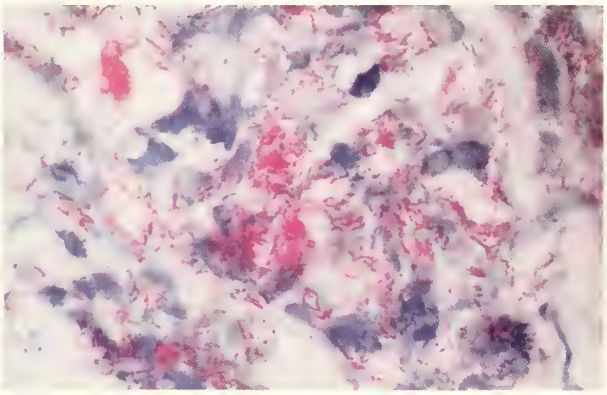

Figure 5.—The dermis in lepromatous leprosy shows foam cells (hematoxylin and eosin stain).

TABLE 2.—*Recommendations for Therapy in Adult Patients With Leprosy*

Source	Treatment of Leprosy: Tuberculoid	Treatment of Leprosy: Lepromatous
World Health Organization	Dapsone, 100 mg/day, and rifampin, 600 mg/mo for 6 mo	Dapsone, 100 mg/day, with clofazimine, 50 mg/day, and supervised rifampin, 600 mg plus clofazimine, 300 mg/mo; therapy to be continued at least 2 yr or until smears negative (generally 5 yr)
Gelber.....	Dapsone, 100 mg/day for 5 yr	Dapsone, 100 mg/day for life, and rifampin, 600 mg/day for 3 yr

the loss of *M leprae* viability and is far more rapid, becoming zero in days or weeks with rifampin treatment and in a few months with dapsone use.

Reactional States in Leprosy and Their Treatment

During the course of lepromatous leprosy, patients may have a reaction, generally while on therapy, erythema nodosum leprosum or lepra type 2 reaction. This syndrome consists of one or a number of the following manifestations: painful papules of the skin that may ulcerate, fever, neuritis, lymphadenitis, orchitis in men, uveitis, glomerulonephritis with red cells and red cell casts in the urine, and occasionally arthritis, particularly of large joints. Erythema nodosum leprosum is histologically a vasculitis or panniculitis thought to be due to immune complex deposition. The inciting antigen is probably an *M leprae* constituent that is released as the organisms are being killed. Patients with lepromatous leprosy have a diffuse hyperglobulinemia that results in a wide variety of false-positive serologic tests, including VDRL, antinuclear antibodies, and rheumatoid factor. The syndrome of erythema nodosum leprosum may be variable. Patients may experience one or several episodes that may be either mild or severe. In some cases, skin lesions of erythema nodosum leprosum may pustulate and ulcerate, with fevers as high as 40.6°C (105°F) developing.

If episodes of erythema nodosum leprosum are mild, they may be treated symptomatically only with aspirin. On the other hand, if severe symptoms occur, prednisone in doses of 40 to 60 mg a day may be required. Alternatively, though its onset of action requires several days, thalidomide in a dose of 100 to 300 mg nightly has proved as effective as prednisone in controlling erythema nodosum leprosum. The activity of thalidomide for this reactional state was found serendipitously in a leprosarium in Israel where a physician regularly administered thalidomide for its original sedative properties to his patients and happened to note that patients were no longer having erythema nodosum leprosum with its previous fre-

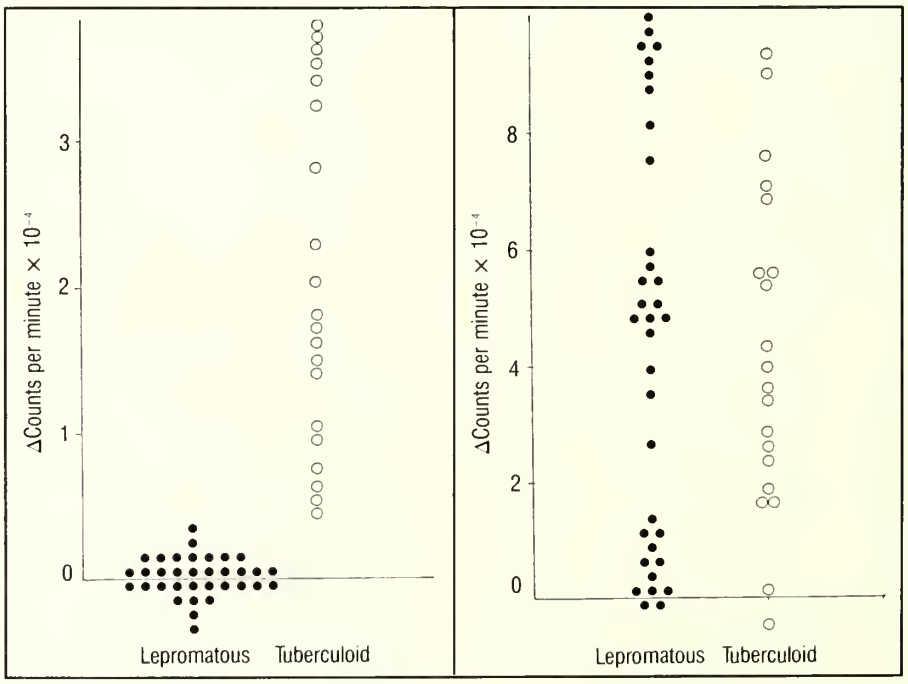

Figure 6.—The lymphoproliferative response of patients with lepromatous leprosy (n = 34) and those with the tuberculoid form (n = 20) is shown to, **left**, *Mycobacterium leprae* antigen and, **right**, purified-protein-derivative antigen, in both cases using 1 μg per culture. The findings demonstrate the *M leprae*-specific anergy of lepromatous leprosy.

quency. Before the recognition that it caused severe birth defects, particularly phocomelia, when given to pregnant women, thalidomide was considered the ideal tranquilizer, principally because the median lethal dose for thalidomide is almost infinitely large. For men and nonpregnant women, thalidomide is safe, with its only side effects other than tranquilization being mild leukopenia, constipation, and rare peripheral neuropathy affecting shoulder and particularly hip girdle strength. It has been postulated that thalidomide is active in erythema nodosum leprosum and perhaps other immunologically mediated disorders by impairing immunoglobulin M synthesis, polymorphonuclear leukocyte migration, and the production of tumor necrosis factor.[32,33] For lepromatous leprosy, thalidomide is available for the control of erythema nodosum leprosum in men and nonfertile women under an investigational license held at the G.W. Long Hansen's Disease Center with coinvestigators at a number of regional centers, including the four on the West Coast.

Patients in the middle of the spectrum either before therapy (downgrading reaction) or after the initiation of therapy (reversal reaction) may have another sort of reaction, a lepra type 1 reaction, associated with signs of inflammation in old borderline lesions, the development of new inflamed skin lesions, neuritis, and low-grade fever. These reactions can only be treated with corticosteroids—generally 40 to 60 mg per day of prednisone initially—on which therapy patients must be maintained (preferably at lower levels) for a few months after control lest recurrence occurs. For this reason, steroid therapy should be initiated only for lepra type 1 reactions in the presence of neuritis, skin inflammation that threatens to ulcerate, or if cosmetically important sites, such as the face, are involved. The initiation of steroids within 24 hours of such a reaction involving nerves is required to prevent irreversible sequelae and is one of the few medical emergencies in patients with leprosy.

Patients with a form of leprosy known as diffuse lepromatosis, which is almost exclusively found in western Mexico, in which they generally have no visible nodules but diffuse dermal thickening, may have a distinct reaction called Lucio's phenomenon. Shallow ulcerations develop on the lower extremities that, when multiple, commonly result in secondary infection, bacteremia, and death due to sepsis. It is not clear if this is a regional variant of erythema nodosum leprosum or a result of small arteriolar occlusion.[34] For this reaction, although steroids may be of some benefit, neither corticosteroids nor thalidomide have proved reliably effective. Because Lucio's phenomenon may be the result of immune complexes, particularly cryoglobulin complexes, exchange transfusion for severe cases has been recommended.[35] Because death results from bacteremia, we have found careful wound care and appropriate antimicrobials effective.

Serologic Tests in Leprosy

In 1981 Hunter and Brennan found that *M leprae* contained a specific phenolic glycolipid, its terminal trisaccharide and particularly its terminal glucose being unique among mycobacteria and, indeed, in nature.[36] In patients with leprosy, antibodies develop to this phenolic glycolipid, mainly of the immunoglobulin M class. We found that lepromatous patients almost invariably (96%) had this antibody, whereas patients with other mycobacterial diseases, whether tuberculosis or atypical mycobacterial infections, did not.[37] Unfortunately, in patients with tuberculoid leprosy, in whom we often do not find organisms and at times have difficulty distinguishing from patients with other types of granulomatous dermatitis, only about two thirds of the time are these antibodies present.

There is generally a fall in antibody titer with effective treatment, untreated lepromatous patients having a higher mean antibody titer than those who have had several years of therapy.[37] The rate of fall of titers after the initiation of effective treatment in individual patients is so variable that the usefulness of monitoring titers to assess the efficacy of therapy is limited. On the other hand, when a precipitous rise in titers occurs, this has been found to coincide with disease relapse.[37] Unfortunately, a loss of antibody to *M leprae*-specific phenolic glycolipid cannot be used as a measure of cure because patients who have been treated for many years and who no longer harbor detectable *M leprae* in the skin may still frequently have significant, though low, levels of antibody.[37]

Another area where serologic tests may prove useful is in identifying patients incubating disease before clinical manifestations. Unfortunately, in many locales there is a high prevalence of serum antibody to this phenolic glycolipid that, if used to select patients for the initiation of therapy, would result in the treatment of a considerable number of persons who might never get the disease to prevent it developing in a few. Prevalence of the antibody in a population, however, may prove the most sensitive assessment of *M leprae* transmission within a population and consequently provide the means to monitor the rise and fall of endemicity. The prevalence of antibody in a population vaccinated against leprosy may also provide the most sensitive means currently available to monitor vaccine efficacy.

Vaccine Prophylaxis

Bacille Calmette-Guérin vaccination for the two major mycobacterial diseases, tuberculosis and leprosy, has demonstrated variable efficacy. For leprosy it is moderately to minimally effective.[38-42] Because there is considerable evidence that mycobacterial lipids and sugars, particularly phenolic glycolipid and lipoarabinomannan,[17-19] inhibit both lymphocytic and macrophage function, we have postulated that protein molecules of *M leprae* devoid of these immunosuppressive molecules may prove to be superior vaccines against *M leprae* and, by analogy, also perhaps against *M tuberculosis*. Indeed, we have found that certain *M leprae* proteins including various cell wall protein preparations, soluble proteins, partially purified proteins, and bioengineered proteins, when used as vaccines in mice, afford protection against subsequent *M leprae* infection, and certain of these provide a protection that is consistently more effective and

longer lasting than killing *M leprae* itself.[43,44] These studies provide hope that in the future a newer generation of *M leprae* human vaccines based on *M leprae* proteins may prove superior to bacille Calmette-Guérin vaccine and generally efficacious.

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Graves' Ophthalmopathy

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Ophthalmopathy develops in about 30% of patients who have Graves' disease. The pathogenesis, like that of the hyperthyroidism, is probably autoimmune in nature. The eye manifestations are diverse and include lid lag, soft tissue swelling, proptosis, corneal damage, diplopia, and optic neuropathy. The natural history is benign in 90% of patients, with gradual improvement over time. Therapeutic options include corticosteroid therapy, radiation, and surgical treatment. The last is usually the therapy of choice for severe or disfiguring ophthalmopathy.

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Graves' ophthalmopathy comprises diverse but characteristic ocular manifestations in patients who have Graves' disease. Graves' disease is an autoimmune disorder characterized by the triad of diffuse thyrotoxic goiter, an infiltrative ophthalmopathy, and occasionally a characteristic dermopathy—pretibial myxedema and thyroid acropachy. The individual components may occur together or separately, although dermopathy is rarely seen without ophthalmopathy. I review the pathogenesis, clinical features, and management of Graves' ophthalmopathy.*

Graves' disease is relatively common, with a prevalence and incidence of about 1.0% and 0.1%, respectively. Ophthalmopathy develops in 20% to 40% of patients.[1] Most patients without ophthalmopathy have subtle changes noted on orbital imaging. Female predominance (3:1) is present for both thyroid and eye manifestations. The incidence of disease peaks in the fifth decade. Male sex and older age are associated with more severe ophthalmopathy.[2] In about 85% of patients with ophthalmopathy, symptoms develop within 18 months of the onset of hyperthyroidism.[3] Almost half will present with simultaneous thyroid and eye disease. Eye manifestations are relatively uncommon in Asians.[4]

For the purpose of further discussion, Graves' hyperthyroidism will refer to patients without ophthalmopathy. Graves' ophthalmopathy will refer to patients with eye manifestations and some degree of thyroid abnormality. The rest are considered to have "euthyroid" Graves' disease. Of note, ophthalmopathy will also develop in as many as 5% of patients with Hashimoto's thyroiditis. Synonyms used to describe Graves' ophthalmopathy include thyroid-associated ophthalmopathy and endocrine ophthalmopathy.

*See also the editorial, "The Enigma of Graves' Ophthalmopathy," by R. S. Bahn, MD, on pages 633-635 of this issue.

Pathogenesis

The immediate cause of hyperthyroidism is thyroid-stimulating antibodies to the thyroid-stimulating hormone (TSH) receptor. Less is known regarding the other components of this disease. It is widely accepted that the ophthalmopathy is autoimmune in origin, although its exact details are still under investigation.[5,6] A pathogenic linkage between the eye and thyroid manifestations has not yet been proved. There is no close relationship between the ophthalmopathy and any particular HLA haplotype, except for HLA-DR3 and B8 in whites.[7]

Older theories postulated a role of TSH or its breakdown products or both in the cause of ophthalmopathy. They can cause exophthalmos in the guinea pig harderian (lacrimal gland equivalent) model.[8] This was supported by anecdotal reports of worsening ophthalmopathy when hyperthyroid patients were rendered hypothyroid. These theories have not been supported by research on humans, however. Thyroglobulin-antithyroglobulin antibody immune complexes have been demonstrated on plasma membranes of orbital tissues, but have not been shown to cause cellular damage. There is no correlation between serum antithyroglobulin titer and disease severity.[9] In fact, complete thyroid ablation has generally not been effective in reducing eye disease, with studies having shown mixed results.

Newer theories focus on antibodies directed at orbital myocytes and fibroblasts. Thyroid-stimulating hormone receptor antibodies do not cross-react with eye muscle or orbital connective tissue.[6] Ophthalmic immunoglobulins are frequently found in patients but not controls or those with Graves' hyperthyroidism. Autoantibodies have been detected to both eye muscle and orbital fibroblasts,[10-12] and in most cases antibodies have been heterogeneous. This may account for the variation in eye manifestations and for variable sensitivity and specificity of current assays.

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
TSH = thyroid-stimulating hormone

The relative contribution of orbital myocytes and fibroblasts is debated. At autopsies or operations, enlarged extraocular muscles—as much as 10 times normal size—are the most striking feature. They are characterized initially by interstitial edema and later fibrosis.[13] Myocytes often appear normal. Likewise, electromyography is normal in most patients, even those manifesting extraocular dysfunction. Fibroblasts, lymphocytes, macrophages, plasma cells, and mast cells are present in increased numbers. Antibody-dependent, cell-mediated cytotoxicity against orbital myocytes is confirmed by in vitro data,[11] but the absence of myocyte destruction in vivo argues against this as the sole mechanism. Both lymphocytes and immunoglobulin G from patients have been shown to stimulate orbital fibroblasts in normal subjects.[14]

Also supporting the fibroblast theory is the strong association with Graves' dermopathy, which is characterized by fibroblast proliferation. The leukocyte procoagulant activity assay has been used to show cell-mediated immunity to eye muscle and thyroid membrane but not orbital connective tissue.[15] There is no evidence for direct cytotoxic T-cell attack, complement-mediated immunity, or immune-complex deposition in the pathogenesis of Graves' ophthalmopathy.

A shared antigen between the thyroid and eye muscle (but not skeletal muscle) has recently been identified. Antibodies against this 68-kilodalton antigen have been noted in most patients.[16] Further data are pending.

Aberrant HLA-DR expression on orbital tissues may play a role in pathogenesis. Genes of the major histocompatibility complex class II antigens (HLA-DR) are normally expressed on monocytes, macrophages, B cells, endothelial cells, and activated T cells. Aberrant expression is noted in other autoimmune disorders. Interferon gamma stimulated orbital fibroblast HLA-DR antigen expression in vitro.[17] Medications used in patients with Graves' hyperthyroidism and ophthalmopathy, including methimazole and dexamethasone, have been shown to reduce interferon gamma-induced HLA-DR expression in vitro.[18]

In summary, the pathogenesis of Graves' ophthalmopathy probably involves humoral and cellular mechanisms. Orbital fibroblasts and myocytes are probably both targeted, possibly through different mechanisms. A common antigen remains to be identified. Antibody heterogeneity may explain the variations in eye manifestations. An association of Graves' ophthalmopathy and smoking has recently been noted in several small retrospective studies.[4,19] The cause is unknown, and prospective studies are pending.

Clinical Features

The ocular manifestations of Graves' disease are diverse and may be divided into infiltrative and noninfiltrative. An evaluation includes general appearance, slit-lamp examination, ocular motility, visual acuity, color vision, visual fields, and proptosis measurement. Noninfiltrative signs include widening of the palpebral fissure, lid retraction, and lid lag. These may reverse with treatment of the hyperthyroidism. During the early phases of the disease, lid retraction may reverse with the use of local sympatholytics. The upper eyelid muscles may eventually fibrose (Müller's muscle and levator palpebrae superioris), requiring surgical repair. Lower eyelid retraction occasionally occurs (Collier's sign).

Infiltrative ophthalmopathy results from swelling of retro-orbital soft tissues. The symptoms and signs of Graves' ophthalmopathy are often classified with the "NO SPECS" system (Table 1),[20] which has been used to assess the need for treatment and response to therapy. Other classification schemes assign various values to each class of signs to estimate disease severity, called an ophthalmopathy index.

TABLE 1.—*Abridged Classification of Eye Changes of Graves' Disease**

Class	*Definition*
0	No physical signs or symptoms
I	Only signs, no symptoms (signs limited to upper eyelid retraction, stare, and lid lag)
II	Soft tissue involvement (signs and symptoms)
III	Proptosis (3 mm or more)
IV	Extraocular muscle involvement
V	Corneal involvement
VI	Sight loss (optic nerve involvement)

*From Werner.[20]
†Each class usually but not necessarily includes involvement of the preceding class.

Soft tissue signs and symptoms are the most common manifestation of infiltrative ophthalmopathy. Swelling in the posterior orbit impairs venous drainage. Symptoms include excessive lacrimation, retrobulbar discomfort, photophobia, and a sandy or gritty sensation. Signs include resistance to retrodisplacement of the eye, lacrimal gland enlargement, lid fullness or edema, conjunctival injection, chemosis, and occasionally herniation of retrobulbar fat.

Given the limited orbital space, progressive swelling eventually results in a forward protrusion (proptosis or exophthalmos). Measurements are made by Leudde, Krahn, or Hertel exophthalmometers. For the Hertel measurement, the upper limit of normal is 18 mm in whites and 21 mm in blacks. There is normally 1 mm or less difference between eyes. Patients or family complain of a "staring" or "wild" expression. Retrobulbar pain may be present. Severe proptosis may result in lagophthalmos (incomplete lid closure) and cause corneal drying, exposure keratitis, or ulceration. An elevated intraocular pressure on upward gaze is common. This usually returns to normal with normal gaze and does not require therapy.

Extraocular muscle involvement is commonly seen on computed tomographic (CT) scans, although few people

clinically manifest muscle dysfunction. Inferior and medial recti are most commonly involved. Paresis, limitation of motion, and occasionally fixation may occur. Diplopia is common because the limitation is usually asymmetric. Diplopia may be intermittent or constant and may occur in the horizontal, vertical, or oblique positions. An edrophonium chloride (Tensilon) test should be done to rule out myasthenia gravis. Interestingly, Graves' ophthalmopathy develops in about 5% of patients who have myasthenia gravis, and vice versa 0.2%.[21]

This association may be the result of similar cell surface receptors or targets. Of note, thyroglobulin and acetylcholinesterase share extensive amino acid homology.[22]

Optic neuropathy develops in less than 5% of patients with Graves' disease.[23] Most cases are slowly progressive and bilateral, but 15% of cases are unilateral. Occasionally optic neuropathy is acute and rapidly progressive. Papilledema, retinal hemorrhage, afferent pupillary defects, central scotomas, and other visual field defects may be seen. Optic neuropathy occurs when swollen eye muscles compress the nerve at the orbital apex (the conus syndrome). Visual acuity and color vision are impaired. Proptosis need not be present.[21]

Diagnosis

The diagnosis of Graves' ophthalmopathy is based on the triad of characteristic eye findings, thyroid dysfunction, and imaging studies. Between 5% and 10% of patients will be euthyroid, although on further testing many of these will manifest some abnormality—abnormal thyroid-releasing hormone stimulation test, triiodothyronine suppression test, antithyroid antibodies, and TSH antibody. Some argue that imaging is not necessary if a patient's symptoms are bilateral and classic.

The differential diagnosis is broad and includes malignant neoplasms—primary orbital tumors, lymphoma, and metastatic disease—vascular anomalies, orbital pseudotumor, vasculitides, sarcoidosis, amyloidosis, and orbital infections such as cellulitis or trichinosis. These can usually be distinguished by orbital imaging procedures. When a patient is euthyroid, and especially when only one eye is affected, these other causes are important to rule out. Some patients require orbital venography, cerebral arteriography, or orbital biopsy. Eyelid retraction is almost pathognomonic but may also be seen in midbrain disease (Parinaud's syndrome), aberrant regeneration of the third cranial nerve, previous surgical procedure of the eyelid, and the use of sympathomimetic drugs.[24]

Computed tomography is currently the imaging study of choice.[1] It effectively excludes retrobulbar tumors. Even when the clinical presentation is unilateral, CT usually shows bilateral involvement. The most characteristic change is extraocular muscle enlargement. The muscle tendons are typically spared in Graves' ophthalmopathy, unlike in orbital myositis or pseudotumor. Some centers have used orbital ultrasonography to monitor disease activity, but this is not generally available. Magnetic resonance imaging has not been shown superior to CT.[22]

Natural History

Little has been written about the natural course of Graves' ophthalmopathy. The disease is usually most severe at the beginning. Noninfiltrative signs may abate after the hyperthyroidism is treated. Severe eye signs develop in about 10% of patients with ophthalmopathy. Most gradually resolve with time, although proptosis tends to remain stationary or worsen slightly (1 to 3 mm). When eye findings worsen, it usually occurs within two years of the treatment of the hyperthyroidism. Disfiguring or vision-threatening signs generally do not spontaneously resolve. The effect of continued abnormal thyroid function on the severity of the ophthalmopathy is controversial.[24,25]

One major controversy has been the effect of various antithyroid therapies on the course of the ophthalmopathy. Some investigators have shown that the administration of radioactive iodine (iodine 131) worsens ophthalmopathy relative to an operation or medications,[26,27] whereas others have not.[28,29] Administering radioiodine has been shown to transiently elevate antithyroid antibodies. Anecdotal reports have noted worsening ophthalmopathy after radioiodine was given. Propylthiouracil and methimazole have been shown to suppress these antibodies. Antibody titers do not correlate well with ophthalmopathy, however. Studies have been plagued by small size, a lack of prospective and controlled trials, and difficulty qualitatively evaluating the response to treatment.

Sridama and DeGroot provided the largest study on the effect of antithyroid therapy.[28] They reviewed the course of 537 patients over 11 years. Patients received subtotal thyroidectomy (n = 164), radioiodine therapy (n = 241), or medical therapy (n = 182) for hyperthyroidism. Between 40% and 50% in each group had ophthalmopathy, which was considered severe in 12% to 16% of the patients. Mean proptosis measurements were 21 to 22 mm, and extraocular muscle involvement was present in 1% to 2% of patients. New eye signs developed in 5% to 7% of each group after therapy. Patients with baseline ophthalmopathy worsened in 20% of cases and improved in 13%, again without a substantial difference between treatment groups. The presence of hypothyroidism was not associated with worsening of the ophthalmopathy. Some argue that complete thyroid ablation (total thyroidectomy) would relieve the ophthalmopathy.

Bartalena and co-workers did a prospective study on the prevention of ophthalmopathy progression after the administration of radioiodine.[30] They compared placebo with low-dose prednisone therapy. None of the patients in either group without baseline ophthalmopathy had eye manifestations after receiving radioiodine. In the placebo group, ophthalmopathy worsened in 56% and remained stable in 44%. In the steroid-treated group, ophthalmopathy abated in 52% and remained stable in 48%. There was substantial improvement in patients with baseline ophthalmopathy given a low-dose prednisone regimen.This is not currently the standard of care but may become so if supported by future studies.

Management

The goals of therapy include pain relief, the protection of vision, and cosmetic improvement. Patients should be reassured that it is generally a self-limited illness, yet understand it will require close follow-up. Hyperthyroidism should be corrected and hypothyroidism avoided. Major therapeutic options include corticosteroid treatment, irradiation, surgical intervention, or a combination of these (Table 2). There is considerable controversy over the use of nonsurgical methods. Fortunately, most patients have mild to moderate symptoms and do not require these measures. Ocular dryness can be managed with eye drops during the day and ointment or adhesive tape at night. Temporary tarsorrhaphy may be necessary. Wearing dark glasses reduces photophobia. Congestive signs and symptoms may lessen with elevating the head of the bed or a trial of diuretics. Mild diplopia may respond to prisms in eyeglasses.

TABLE 2.—*Management of Graves' Ophthalmopathy*

Symptoms or Signs	*Management Options*
Soft tissue involvement	
Eye irritation or dryness	Administer artificial tears
Photophobia	Wear dark glasses
Periorbital swelling	Elevate head of bed, diuretics, corticosteroids or radiotherapy
Diplopia	
Mild	Observation or prisms
Severe	Extraocular muscle operation
Proptosis	
Mild	Observation or tarsorrhaphy
Severe	Orbital decompression
Corneal involvement	Lid operation versus orbital decompression
Optic neuropathy	Corticosteroids, radiotherapy, orbital decompression

The goal of immunosuppressive therapy is to reduce swelling and control symptoms until remission occurs. Corticosteroid therapy is the mainstay and is usually given orally or intravenously. Retrobulbar administration can reduce systemic toxicity but is limited by pain and an increased risk of glaucoma. Steroids effectively resolve soft tissue signs and optic neuropathy.[31] Kendall-Taylor and colleagues treated 11 patients with pulsed methylprednisolone, followed by one month of tapering doses of prednisone.[32] All but 1 responded within 24 hours, and 9 of 11 were still improved at six months. Corticosteroid therapy is less effective in patients with long-standing ophthalmopathy, probably because fibrosis occurs. Extraocular muscle signs and proptosis usually do not respond. Severe ophthalmopathy often requires the long-term use of steroids, resulting in substantial side effects.

Other immunosuppressive agents are used less. Cyclosporine therapy has not produced consistent improvement, though it may have an additive effect with prednisone.[33] Ciamexon, a new immunomodulator, has not been shown effective.[34] Therapy with cyclophosphamide and azathioprine has not shown consistent improvement. Plasmapheresis may help some for whom standard therapy has failed, although data are controversial.[35] Several small studies have shown the use of bromocriptine to be effective; the mechanism is unknown.

Orbital radiotherapy has been available for many years, but its use remains controversial. The standard dosage is 20 Gy in ten fractions over two weeks. Reports have varied from minimal to substantial benefits. Higher doses have been associated with radiation retinopathy. As with corticosteroid therapy, optic neuropathy and congestive signs respond better than proptosis and diplopia. In many studies, radiotherapy has been used in combination with steroids or as a salvage therapy for patients in whom steroid or surgical treatment has failed. Donaldson and associates treated 23 patients with irradiation.[36] Of these, 15 (65%) had excellent or good results; improvement occurred within two weeks. None of the patients worsened, and only one relapsed. Patients with long-standing ophthalmopathy were not improved. Other studies have shown lower response rates, however.

Surgical therapy plays a major role in the management of severe or disfiguring ophthalmopathy. Orbital decompression, extraocular muscle operation, eyelid repair, and blepharoplasty are the four main procedures. An operation is needed in fewer than 10% of patients. It should generally be delayed until the patient has been euthyroid with stable eye signs for three to six months. Occasionally the delay is not possible, as in patients with acute progressive optic neuropathy. Often more than one type of surgical procedure is necessary. A specific sequence must be followed: orbital decompression, extraocular muscle repair, and eyelid repair, followed by blepharoplasty.

Orbital decompression effectively treats proptosis, corneal ulceration, and optic neuropathy. The transantral approach is preferred for most patients with progressive optic neuropathy. It combines orbital floor and medial wall resection. Recently a transorbital approach—removal of the lateral wall, medial wall, and floor—has been used alone or in combination with the transantral approach.[21,37] There is generally a 4- to 7-mm initial decrease in proptosis, followed by 1 to 2 mm over the next two months. The presence of sinusitis is a contraindication. The major side effect is diplopia. Preoperative diplopia is not lessened by this operation, and as many as 40% to 50% of patients without baseline diplopia have symptoms or signs postoperatively. Rare side effects include sinusitis, cerebrospinal fluid rhinorrhea, meningitis, and antral-oral fistulae. Pneumoproptosis may occur due to ethmoidal air cell rupture, but it rapidly subsides. Hallin and co-workers reported on 25 patients with optic neuropathy treated by transantral decompression.[38] Visual acuity, color vision, and visual fields each improved in about 75%, remained unchanged in 20%, and worsened in 5% of patients. New diplopia developed in 7 of 12 patients. Proptosis, extraocular muscle limitation, and CT findings did not correlate with outcome. Others have reported similar or slightly better results, with patients oc-

casionally receiving radiation therapy postoperatively. Some authors recommend a trial of corticosteroids before surgical intervention for optic neuropathy.[39]

The goal of extraocular muscle repair is binocular vision in the primary and reading positions. Patients with intermittent diplopia or symptoms only on extreme lateral or upward gaze should be counseled to forgo the procedure. About 60% will be corrected with one operation, and 10% require three or more. Patients are generally left with a limited range of eye motion and a "tunnel" of binocular vision that gradually enlarges with time. Some patients will benefit from prisms placed in their glasses.

Minor upper eyelid retraction can be corrected by a Müller's myotomy, resulting in a 2- to 3-mm release. Extensive upper lid retraction is treated by a graded tenotomy of the levator palpebrae superioris with a "spacer" (scleral graft) inserted and recession of the levator tendon.[40] Lower lid retraction is also corrected by introducing a spacer. Ptosis results in less than 10% of upper eyelid repairs and is easily corrected. After an eyelid operation, patients may undergo blepharoplasty to remove excess skin and soft tissue (due to previous swelling).

Summary

Graves' ophthalmopathy is a complex orbital disease of unknown cause. The manifestations are diverse, ranging from mild eye irritation to blindness or severe disfigurement. The pathogenesis and natural history are still uncertain, although most agree that it is an autoimmune disease. Fortunately, most cases are mild and gradually resolve without therapy. Approximately 10% of cases are severe. Therapy is aimed at either shrinking orbital contents or expanding the orbit. Current options include corticosteroids, radiation therapy, and surgical intervention. Patients require a tailored approach, and combined therapies may be necessary.

Early detection, intervention, and referral are important. The differential diagnosis of proptosis or ophthalmopathy requires the consideration of malignant tumors, infections, and collagen vascular disorders. An early evaluation may detect previously undiagnosed hyperthyroidism. Reassurance and education are important, as this condition can cause considerable distress.

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Articles

Health Care Use by Frequent Marijuana Smokers Who Do Not Smoke Tobacco

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Even though marijuana smoke contains carcinogens and more tar than tobacco smoke and marijuana intoxication has been implicated as a risk factor for injuries, relatively little epidemiologic evidence has identified marijuana use as a risk factor for ill health. This study is the first to examine the health effects of smoking marijuana by comparing the medical experience of "daily" marijuana smokers who never smoked tobacco (n = 452) with a demographically similar group of nonsmokers of either substance (n = 450). Marijuana smoking status was determined during multiphasic health checkups at Kaiser Permanente medical centers between July 1979 and December 1985. Medical records were reviewed for as long as 2 years after the checkups. Frequent marijuana smokers had small increased risks of outpatient visits for respiratory illnesses (relative risk [RR] = 1.19; 95% confidence interval [CI] = 1.01, 1.41), injuries (RR = 1.32; CI = 1.10, 1.57), and other types of illnesses (RR = 1.09; CI = 1.02, 1.16) compared with nonsmokers; their risk of being admitted to a hospital was elevated but not statistically significant (RR = 1.51; CI = 0.93, 2.46). Analyses were adjusted for sex, age, race, education, marital status, and alcohol consumption. Daily marijuana smoking, even in the absence of tobacco, appeared to be associated with an elevated risk of health care use for various health problems.

(Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD: Health care use by frequent marijuana smokers who do not smoke tobacco. West J Med 1993; 158:596-601)

Marijuana is the most widely used illicit recreational drug in the United States. Marijuana smoke contains carcinogens and more tar than tobacco smoke, and the psychoactive effects of marijuana ingestion have been implicated as a risk factor for injuries. Yet, surprisingly little epidemiologic evidence is available concerning the possible effects of smoking marijuana on respiratory health, injury risk, or other health conditions.*

As a pilot project for a larger study of the health consequences of smoking marijuana, we compared the medical experience of persons who self-reported frequent marijuana smoking but who never smoked tobacco with that of a demographically matched group who reported never smoking tobacco or marijuana. To our knowledge, this study is the first to review the medical records of a large number of non-tobacco smoking marijuana users.

Subjects and Methods

Study Population

Study subjects were selected from members of the Kaiser Permanente Medical Care Program who had at least one multiphasic health checkup (MHC) at the Oakland or San Francisco, California, medical centers between July 1979 and December 1985. The multiphasic health checkup was completed by about 30,300 persons per year during the study period; the examination was discontinued at San Francisco in 1980. The MHC population has been described previously and has provided the data for numerous studies of smoking and drinking habits.[1,2] The Kaiser Permanente membership is demographically and socially heterogeneous, reflecting the diversity of the San Francisco Bay Area population, but impoverished and undereducated persons are underrepresented.[3] Persons who take the MHC tend to be more health conscious and better educated than Kaiser Permanente members in general.[4,5]

The MHC examinees were given several questionnaires documenting demographic and social characteristics, medical history, health habits, the use of tobacco and marijuana (questionnaire administered from July 1979 to 1986), and the use of alcohol (questionnaire administered from 1978 to 1985). About 86% of the examinees completed the tobacco or marijuana use questionnaire, and 80% completed the alcohol use questionnaire.

Definitions of Study Groups

About 14,600 respondents to the tobacco-marijuana survey during the study period reported smoking mari-

*See also the editorial by D. P. Tashkin, MD, "Is Frequent Marijuana Smoking Harmful to Health?" on pages 635-637 of this issue.

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ABBREVIATIONS USED IN TEXT

CI = confidence interval
MHC = multiphasic health checkup
RR = relative risk

juana more than six times in their lifetimes and that they currently smoked marijuana. Among these persons, a group of 746 marijuana smokers reported smoking marijuana almost every day and never smoking tobacco. We defined the first MHC at which the tobacco-marijuana survey was completed as the index MHC for the marijuana smoking group. We selected a comparison group of nonsmokers from respondents who reported never smoking marijuana or tobacco. For each marijuana smoking subject, we attempted to match a nonsmoker by sex, age (birth year), race (Asian, African American, white), and index MHC date (within a month). We initially matched controls with 709 marijuana smokers. To control for varying lengths of Kaiser Permanente membership, we selected for study those pairs in which both members were enrolled in Kaiser for either at least one or at least two years after the index MHC. This process left 486 pairs for whom medical charts were reviewed (65% of the 746 original marijuana smokers). An additional 70 persons were excluded from this report because of the unavailability of an alcohol questionnaire after December 1985. The final sample thus consisted of 452 marijuana smokers and 450 nonsmokers.

Data Sources

The index MHC questionnaire provided information on sex, age, race, education, and marital status; self-reported health status (a checklist of 34 medical conditions); the existence of serious illnesses; hospital admissions in the past year; and the presence of problems with drugs. Data on marijuana and tobacco use, duration of marijuana use, and number of days ill with a cold, flu, or sore throat were obtained from the supplemental tobacco-marijuana survey. We used a drinking status measure derived in previous studies from items regarding quantity and frequency of drinking on the alcohol survey.[6] Six drinking categories were defined for this study: abstainer, ex-drinker, occasional (<1 drink per month), less than one drink per day but more than one per month, one to two drinks per day, and three or more drinks per day. The small number of ex-drinkers was combined with abstainers in the main analyses.

Kaiser Permanente outpatient medical records were reviewed by two trained medical records technicians who were unaware of subjects' marijuana smoking status. The medical records of each pair of subjects were reviewed for the same follow-up period, which was either one or two years after the index MHC date, depending on the length of membership in the Kaiser program. Following a written protocol, records reviewers identified all office visits to a physician or nurse practitioner. Prenatal visits were excluded, as were telephone contacts, letters, and visits for procedures only, such as ultrasonograms. As many as three illnesses were coded as reasons for the visit, using the International Classification of Diseases, 9th Revision, codes.[7] Each visit was assigned to one of three categories for this report: respiratory conditions (codes 460 to 519), injuries and poisonings (codes 800 to 999), or other diseases and conditions (all other codes). If more than one, the reason listed first was used. Inpatient data were obtained from Kaiser Permanente computer-based hospital admission files. All hospital admissions were included. Because of the small number of hospital admissions during the follow-up period, we combined all diagnoses in the analysis.

Analysis

Differences in the distribution of baseline characteristics were evaluated with χ^2 tests. Poisson regression was used to estimate the relative risk for the marijuana smoking group versus the nonsmoking group of outpatient visits or hospital admissions. The matched-pairs design was dropped in the analysis, and the variables used for matching were instead controlled statistically to avoid dropping both members of a pair when only one member was missing data on a covariate. Covariates in each regression model included alcohol consumption, age, sex, race, educational level, and marital status. Terms for marijuana exposure interacting with drinking status were introduced to examine possible interaction effects. The SAS statistical analysis package was used for all analyses.[8]

Results

Characteristics of the marijuana smokers and the nonsmokers at the time of the index MHC are compared in Table 1. Marijuana smokers had a lower educational level and were less likely to be married than nonsmoking subjects. Alcohol drinking levels differed dramatically between the two groups, with marijuana smokers being more likely to drink alcohol and (among current drinkers) to drink more heavily. Marijuana smokers reported more days ill with a cold, flu, or sore throat in the past year and were more likely than the nonsmoking group to report having a serious problem with drugs.

A total of 6,088 visits were recorded, including 3,206 among the marijuana smoking group and 2,882 among the nonsmoking group. At least one outpatient visit for respiratory problems was made by 36% of the marijuana smokers versus 33% of the nonsmokers, 39% versus 28% made at least one visit for injury, and 94% versus 93% made at least one visit for other reasons. After adjustment for covariates, the marijuana smoking group showed small but statistically significant increased risks of outpatient visits for all three categories of conditions (Table 2).

Interaction between marijuana smoking and alcohol consumption was significant in relation to visits for injury and for other reasons but not in relation to visits for respiratory problems. The percentage distributions of visits for injury (none versus ≥1) by drinking level suggest that the generally higher injury risk for the marijuana smoking group compared with the nonsmoking group was reduced in the heaviest drinking level (Table 3). For other dis-

TABLE 1.—*Self-reported Characteristics of Marijuana Smokers (n = 452) and Nonsmokers (n = 450) at Index Multiphasic Health Checkup, July 1979 to 1985 (%)*

Characteristic	Marijuana Smokers, %	Nonsmokers, %
Sex		
Female	32.7	33.1
Male	66.3	66.9
Age, yr		
<25	35.4	36.2
25-34	48.0	46.2
≥35	16.6	17.6
Race		
Asian	2.0	2.0
African American	36.9	37.3
White	61.1	60.7
Educational level		
High school or less	22.4*	15.6*
Some college or vocational	42.5	40.9
College graduate or more	33.0	41.8
Missing data	2.2	1.8
Marital status		
Married	29.4†	44.0†
Separated, divorced, widowed	11.3	7.3
Never married	57.3	46.9
Missing data	2.0	1.8
Alcohol drinking status		
Never drank	2.4†	20.2†
Former drinker	0.9	3.1
Current drinker		
<1 drink/mo	10.6	27.3
>1 drink/mo, <1/day	42.7	36.7
1-2 drinks/day	27.4	10.0
≥3 drinks/day	15.9	2.7
Current problem with drugs?		
Yes	5.8†	0.0†
No	92.7	98.2
Missing data	1.6	1.8
Number of health conditions (34 possible)		
None	23.0	29.1
1-4	58.6	53.1
≥5	16.8	16.0
Missing data	1.6	1.8
Mean (SD)	2.5 (2.5)	2.2 (2.7)
Days ill with cold, flu, sore throat in past year		
None	25.0*	33.1*
1-5	49.3	44.7
≥6	24.1	21.6
Missing data	1.6	0.7
Serious illness in past year?		
Yes	10.8	7.1
No	86.3	90.9
Missing data	2.9	2.0
Admitted to hospital in past year?		
Yes	4.9	6.0
No	92.9	91.6
Missing data	2.2	2.4
Duration of marijuana use, yr		
<5	19.0	--
5-9	33.6	--
10-14	36.3	--
≥15	9.5	--
Missing data	1.5	--

*$P < .05$. †$P < .001$.

eases, the difference in risk was higher in the nondrinking and heaviest drinking levels (Table 3).

The duration of marijuana smoking was associated in different ways with the three categories of visits (Table 4). The risk of respiratory visits was significantly elevated for persons who had smoked marijuana for less than ten years, but not for those who had smoked for ten years or more. Among marijuana smokers, there was a negative association between duration of smoking and risk of visits for respiratory problems ($P = .0002$). For injury visits, however, a longer duration of marijuana smoking was associated with a greater risk. Compared with the nonsmoker group, persons who had smoked marijuana for 15 years or more had twice the risk of visits for injury. A test for linear trend was significant ($P = .0001$). For other types of visits, only those who had smoked marijuana for five to nine years had a significantly increased risk compared with the nonsmoker group, and the other duration categories did not follow a consistent pattern.

There were 86 hospital admissions in the two study groups. The relative risk for the marijuana smoking group compared with the nonsmoker group was elevated but not statistically significant (relative risk [RR] = 1.51; 95% confidence interval [CI] = 0.93, 2.46; $P = .10$). A duration of marijuana use of less than five years was of borderline significance (RR = 2.02; 95% CI = 0.98, 4.15; $P = .06$).

TABLE 2.—*Relative Risk (RR) of Outpatient Medical Visits for Respiratory, Injury, and Other Conditions by Marijuana Smokers (n = 452) Versus Nonsmokers (n = 450)**

	Type of Visit					
	Respiratory		Injury		Other	
Marijuana Exposure	RR	95% CI	RR	95% CI	RR	95% CI
Nonsmokers (reference)	1.00	--	1.00	--	1.00	--
Marijuana smokers	1.19	1.01, 1.41	1.32	1.10, 1.57	1.09	1.02, 1.16

CI = confidence interval

*Adjusted for sex, age, race, educational level, marital status, and alcohol consumption.

TABLE 3.—*Percentage Making 1 or More Outpatient Visits for Injury and Other (Nonrespiratory) Causes by Marijuana and Alcohol Use*

		Outpatient Visits					
		Marijuana Smokers			Nonsmokers		
Alcohol Use	No.	Injury, %	Other, %	(n)	Injury, %	Other, %	(n)
Never or former	120	40.0	100.0	(15)	27.6	93.3	(105)
Occasional	171	25.0	95.8	(48)	28.5	98.4	(123)
<1 drink/day	358	40.9	95.3	(193)	28.5	90.9	(165)
1-2 drinks/day	169	37.9	94.3	(124)	24.4	91.1	(45)
≥3 drinks/day	84	47.2	90.3	(72)	41.7	83.3	(12)

There was no significant interaction between marijuana smoking and alcohol use.

Discussion

Although epidemiologic studies concerning the health consequences of smoking marijuana are relatively few, a long-term use of marijuana has been implicated as a possible hazard to mental, pulmonary, immune, and reproductive functioning,[9] and marijuana intoxication has been implicated as a risk factor for accidents and injuries.[10] Because marijuana is usually ingested by smoking, possible respiratory effects have naturally been the most frequently investigated.

Compared with tobacco smokers, marijuana smokers typically smoke fewer cigarettes per day but consume more of the cigarette, inhale longer and more deeply, and retain the smoke longer in the lungs.[11] This probably explains why the respiratory deposition of tar and adsorption of carbon monoxide in experimental subjects were four and five times higher, respectively, after smoking marijuana than after smoking tobacco.[12] Because of the high prevalence of cigarette smoking among marijuana smokers, however, it has been difficult to assess the independent association between marijuana smoking and respiratory disease, including lung cancer.[13] Marijuana use has been linked to respiratory problems.[14-17] In one study, heavy smokers of marijuana, whether or not they also smoked tobacco, reported more chronic bronchitis symptoms and more acute bronchitis episodes than nonsmokers of either marijuana or tobacco.[15] Heavy marijuana smoking, with or without concomitant tobacco smoking, appears to affect large (but not small) airway function adversely and to produce histologic lesions in the airways.[15,16,18] A positive association between smoking "nontobacco cigarettes" (presumed to be marijuana) and respiratory symptoms in smokers and nonsmokers of tobacco was reported in a population survey in Tucson, Arizona. Lung function was decreased among male—but not female—smokers of nontobacco cigarettes more than among tobacco smokers.[19]

Marijuana has repeatedly been found to be the second most common drug, after alcohol, present in the blood of nonfatally and fatally injured persons,[20,21] although the role marijuana may play in injury-producing events remains uncertain.[22] Laboratory studies have shown decreased driving-related skills after smoking marijuana.[10] In one experimental study, driving performance declined substantially after ingesting marijuana and alcohol together, but did not decline after taking either substance alone.[23]

In a Swedish study following a cohort of 45,540 male military conscripts for 15 years, heavier cannabis users had a nearly three times greater risk of death than nonusers, but the association did not remain statistically significant after control for the use of alcohol, other drugs, and social background variables.[24] In another study of the same Swedish cohort, heavier cannabis users had an elevated risk of schizophrenia compared with nonusers, even after adjusting for psychosocial covariates.[25]

As the first evidence based on medical records of nontobacco smoking, daily marijuana users, our results make a unique contribution to the growing research on the harmful health effects of marijuana. Our finding of an increased risk of respiratory-related outpatient visits expands the evidence suggesting that frequent marijuana smoking may increase the risk of respiratory illness independent of tobacco smoking. Marijuana smokers in our

TABLE 4.—*Relative Risk (RR) of Outpatient Medical Visits for Respiratory, Injury, and Other Conditions by Duration of Marijuana Smoking (n = 895)**

	Type of Visit					
	Respiratory		Injury		Other	
Duration of Marijuana Exposure, yr	RR	95% CI	RR	95% CI	RR	95% CI
Nonsmokers (reference)	1.00	--	1.00	--	1.00	--
<5	1.40	1.07, 1.83	1.10	0.83, 1.47	0.99	0.89, 1.11
5-9	1.34	1.07, 1.67	1.25	0.99, 1.58	1.26	1.16, 1.38
10-14	1.12	0.90, 1.39	1.35	1.07, 1.68	1.02	0.94, 1.12
≥15	0.91	0.61, 1.35	1.99	1.43, 2.76	0.93	0.79, 1.08

CI = confidence interval

*Adjusted for sex, age, race, educational level, marital status, and alcohol consumption.

study also reported a higher prevalence of upper respiratory tract infections compared with nonsmokers. On the other hand, the duration of marijuana smoking appeared to be inversely related to the risk of outpatient visits for respiratory problems. This result was contrary to our expectation and remains an issue for future research. In our data, long-term marijuana smokers may be the "survivors" of a selection process in which persons who experienced respiratory symptoms were more likely to quit smoking marijuana early in the process.

We also found increased risks of injury-related and other (nonrespiratory, noninjury) outpatient visits among marijuana smokers, suggesting that marijuana use may have many adverse health effects. The complex interaction between marijuana and alcohol use in relation to the risk of medical care use in both of these areas underscores the important role of alcohol in combination with marijuana.[26,27] The duration of marijuana use appeared to be positively related to the risk of making injury-related visits. As with respiratory-related visits, this result was unexpected. It is not clear why a longer use of marijuana would be associated with a greater injury risk and a lower respiratory risk, but these results deserve additional study. The duration of marijuana use was not related to the risk of other types of outpatient visits.

Marijuana smokers in our study also tended to have an elevated risk of being admitted to a hospital. Although the association was not statistically significant, it was consistent with our results regarding medical office visits and thus supports the hypothesis that marijuana smoking is associated with adverse health effects.

Several caveats should be noted. We had no data regarding the use of other drugs such as cocaine; if associated with marijuana use, they may account for the observed differences. Only 6% of the marijuana smokers, however, reported having serious problems with drugs at their index MHC.

Another potential problem is our reliance on self-reporting. The use of illegal or socially undesirable substances such as tobacco, alcohol, marijuana, and other drugs may well be underreported.[28] We are unable to assess this possible bias. Our study subjects, however, completed their questionnaires in a health care setting in which confidentiality was assured.

Finally, our study was intended to serve as a pilot "hypothesis-generating" study of marijuana smoking and health. Restricting subjects to nonsmokers of tobacco allowed us to efficiently assess an association between marijuana use and respiratory illnesses independent of tobacco use but at the cost of studying an unrepresentative sample of marijuana smokers, many of whom smoke tobacco.[29]

In summary, daily marijuana smoking appears to be associated with respiratory conditions even among persons who never smoked tobacco. This association is consistent with a possible independent deleterious effect of marijuana smoking on respiratory health. Frequent marijuana use also appears to be intimately linked to alcohol consumption as a risk factor for injury-related and other medical care. These data are limited, but a larger study in progress (S.S., principal investigator) should elucidate the joint roles of tobacco and marijuana in relation to respiratory health and of alcohol and marijuana in relation to traumatic injuries and other illnesses. This study will include never users, former users, and current users of marijuana, tobacco, and alcohol and will examine medical experience and mortality over a longer period.

Physicians and other primary care professionals may wish to consider counseling patients who frequently smoke marijuana about the potentially widespread harm its use may entail. In our study, physicians recorded marijuana use in the medical records of only 3% of the marijuana smokers, all of whom smoked daily or almost daily. As evidence of the health consequences of smoking marijuana accumulates, physicians should take note of this possibly important health behavior.

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* * *

HOW TO IMAGINE DEAFNESS

Darken your ears until the tunnels
with their intricate clockwork
are sheathed in pitchy calm.
Hum a little blue, to yourself,

but keep it secret. The small bones
will dip delicately, like willow leaves
that merely brush the water's surface,
in their repose. The small hairs

will lie down together like tentacles.
Listen: the lake stops its lapping
repetition of sibilance
(physicist, Sisyphus, sassafras)

and the great snail unfurls itself,
stretches its tongue longingly
toward the distant echo surge
that must be the heart.

KIM ROBERTS
Washington, DC

Articles

Hepatitis A Vaccination

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The safety and immunogenicity of an inactivated hepatitis A virus vaccine were assessed in 101 healthy adults. Seronegative persons with normal serum aminotransferase levels were grouped according to age: Group 1 (n = 24) and group 3 (n = 22) were between 18 and 40 years of age, and group 2 (n = 25) and group 4 (n = 30) were older than 40 years. Groups 1 and 2 received vaccine on a 0-, 1-, and 2-month schedule (schedule A), and groups 3 and 4 received the vaccine on a 0-, 1-, and 12-month schedule (schedule B). Of the 101 vaccinated subjects, 98 (97%) seroconverted with antibody titers to hepatitis A virus of ≥20 IU per liter after the first dose, and all subjects seroconverted after the second dose. The geometric mean titers a month after the third vaccine dose were significantly greater ($P < .03$) on both schedules for younger subjects (schedule A, 1,743 IU per liter, and schedule B, 7,882 IU per liter) than for older subjects (schedule A, 826 IU per liter, and schedule B, 4,279 IU per liter). Also, the differences in geometric mean titers a month after the third dose were significantly greater ($P < .001$) for subjects in both age groups on schedule B (group 3, 7,882 IU per liter, and group 4, 4,279 IU per liter) than for those on schedule A (group 1, 1,743 IU per liter, and group 2, 826 IU per liter). The hepatitis A virus vaccine was well tolerated, with mild discomfort at the injection site being the main side effect. This vaccine is both safe and highly immunogenic.

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Hepatitis A virus (HAV) infection continues to be a public health problem in the United States. In 1989, about 39,000 cases were reported to the Centers for Disease Control, and this viral infection accounts for as much as 50% of all cases of hepatitis that occur each year in this country.[1] In addition, large epidemics of acute hepatitis A continue to occur. In a recent study from Shanghai, China, more than 300,000 cases of acute hepatitis A resulted from the ingestion of uncooked clams contaminated with HAV.[2]

Several studies have been done recently on the development and testing of HAV vaccines.[3-7] Both attenuated and killed preparations of HAV vaccines have been used, and the preliminary reports on their safety and immunogenicity appear promising. In addition, in a recent report, a single dose of inactivated HAV vaccine was used and showed protective efficacy against clinical hepatitis A in an upstate New York community that was endemic for this disease.[8]

We report herein our experience with a formalin-inactivated HAV vaccine that consisted of the HM175 strain propagated in MRC5 cells. In this study, using a dose of HAV vaccine that had been previously shown to induce a maximal antibody response,[3] we administered vaccine in two different dosing schedules. The immunologic response to the HAV vaccine in two different age groups was assessed.

Subjects and Methods

Staff members from the Huntington Memorial Hospital (Pasadena, California) volunteered for HAV vaccine administration. The inclusion criteria were good health, age 18 years or older, serum tests negative for anti-HAV, normal serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels, and a signed informed consent. Persons who were excluded had received blood, blood products, or immune globulin during the six months before the study, expected to receive blood or blood products or immunosuppressive therapy while enrolled in the study, were enrolled in other vaccine trials, or were lactating or pregnant.

Within seven days of entry into the study, a history was obtained and a physical examination was done on all volunteer subjects. Blood specimens were collected for an initial anti-HAV titer and for tests of liver function. Eligible subjects were randomly assigned to either of two dosing schedules: schedule A: 720 enzyme-linked immunosorbent assay (ELISA) units of the HAV vaccine was administered at months 0, 1, and 2; schedule B: 720 ELISA units was administered at months 0, 1, and 12. Four groups of subjects were studied: subjects 18 to 40 years of age received the HAV vaccine according to either schedule A (group 1) or B (group 3), and subjects older than 40 years received the HAV vaccine according to either schedule A (group 2) or B (group 4).

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ABBREVIATIONS USED IN TEXT

ALT = alanine aminotransferase
AST = aspartate aminotransferase
ELISA = enzyme-linked immunosorbent assay
HAV = hepatitis A virus
HBsAg = hepatitis B surface antigen

At day 0 (month 0), subjects on both schedules were administered HAV vaccine intramuscularly into a deltoid muscle and were observed for 15 minutes for any adverse reaction. A diary card was provided to record any adverse effects occurring within three days after vaccination.

At month 1 (30 ± 7 days after the first dose), the diary cards were retrieved, blood specimens were obtained to measure serum ALT and AST levels and anti-HAV titers, and the second dose of HAV vaccine was administered. The subjects were observed for 15 minutes for any adverse effects and again were provided with a diary card to record any adverse reaction occurring within three days after vaccination.

Subjects allocated to schedule A returned at month 2 (60 ± 7 days after the first dose) for the third dose of HAV vaccine, and the same procedure was followed as at month 1. Additional blood specimens were drawn to measure anti-HAV titers and serum ALT and AST levels at months 3, 12, and 13 (all ± 7 days).

Subjects allocated to schedule B returned at months 2, 3, 12, and 13 (all ± 7 days) to have blood specimens taken for measuring anti-HAV titers and ALT and AST levels. At month 12 (360 ± 7 days after the first dose), after the blood specimens were obtained, a third dose of HAV vaccine was administered. The subjects again were observed for 15 minutes for any adverse effects, and a diary card was provided to record adverse reactions occurring within three days after vaccination. Diary cards were retrieved at months 1, 2, and 13.

Vaccine

The candidate inactivated hepatitis A vaccine (Havrix) used in this study was developed using the HM175 strain of HAV, which was originally derived from human stool and propagated in MRC5 cells according to the seed lot principle.[3] The antigen content of this vaccine has been referenced to a standard by the ELISA and is expressed in ELISA units. This HAV vaccine meets the requirements of the World Health Organization for other inactivated vaccines, such as the poliovirus.[6] Each 1-ml dose contains HAV antigen, 720 ELISA units; aluminum hydroxide corresponding to 0.5 mg of aluminum as the adjuvant; and 5.0 mg of 2-phenoxyethanol added as a preservative. Other excipients include 0.05 mg of polysorbate 20, 3.0 mg of amino acid supplement, 1.15 mg of disodium phosphate, 0.20 mg of monopotassium phosphate, 9.0 mg of sodium chloride, and 0.23 mg of potassium chloride.

Data Analysis

Initially a commercial test kit (HAVAB, Abbott Laboratories, North Chicago, Illinois) was used to determine the presence or absence of anti-HAV in screening blood specimens. The postvaccination serum specimens were sent to SmithKline Biologicals in Rixensart, Belgium, in a blinded manner for the determination of anti-HAV titers by ELISA,[3] and titers were reported in international units per liter. Seroconversion was defined as an anti-HAV titer of 20 IU per liter or higher. The geometric mean titers were calculated by adding together the log of each titer and then determining the anti-log of the mean of the logs. For analysis, the geometric mean titers were compared at several time points for the two age groups using a two-tailed Student's *t* test.

Results

A total of 175 subjects were screened for anti-HAV and serum ALT and AST levels before entry into the study. Of these, 55 were either anti-HAV–positive or had elevated serum ALT or AST levels and were not eligible. Another 14 subjects did not complete the vaccination schedule; that is, they missed one or more vaccinations or missed scheduled appointments to have blood specimens taken and were not included in the final analysis. Another four had adverse reactions to the first dose of vaccination, and one woman became pregnant after two vaccinations, all of whom were withdrawn. The final analysis included 101 subjects who completed the entire series of vaccination and had anti-HAV titers done after each vaccination.

TABLE 1.—*The Demographic Characteristics of 101 Recipients of Hepatitis A Virus Vaccine*

	Schedule A		*Schedule B*	
Demographics	*≤40 yr Group 1*	*>40 yr Group 2*	*≤40 yr Group 3*	*>40 yr Group 4*
Mean age, yr*	30 ± 7	52 ± 5	33 ± 5	46 ± 5
Mean weight, kg (lb)*	66.4 ± 12.7 (146 ± 28)	73.6 ± 17.7 (162 ± 39)	68.6 ± 15.9 (151 ± 35)	69.5 ± 13.6 (153 ± 30)
Men, No.	6	9	5	6
Women, No.	18	16	17	24
Race, No.				
White	11	21	14	28
African American	4	2	3	1
Hispanic	5	1	2	0
Asian	4	1	3	1

*± Standard deviation.

The demographic characteristics for the 101 subjects are shown in Table 1. The average age of the vaccinees was 40 years ± 7 SD. The age, sex, and race for subjects in groups 1 through 4 are also shown.

Eleven subjects had transient increases in serum ALT or AST levels 1.5 times above normal (35 U per liter) on one (7 subjects) or more (4 subjects) occasions during the study. The last four subjects did not have antibodies to the hepatitis C virus when assayed by a second-generation test and were negative for the hepatitis B surface antigen (HBsAg). In all instances, the serum aminotransferase levels returned to normal when tested three months after the HAV vaccination.

Adverse Effects

Transient discomfort at the injection site was reported after 11% of all vaccinations (Table 2). Gastrointestinal symptoms and headaches were infrequent. Most of the side effects were reported after the first dose of HAV vaccine. Injection site discomfort also was experienced after the second and third vaccinations but usually was not reported by the same vaccinees. Four subjects were withdrawn from the study because of an adverse reaction after the first injection of HAV vaccine and were deemed to be unsuitable for further vaccination. These four cases are described in Table 3.

Immunogenicity

Of the 101 subjects, 98 (97%) seroconverted after one dose of HAV vaccine. All subjects seroconverted after two doses of HAV vaccine. At month 2, a month after the second dose of vaccine, there were no significant differences in the geometric mean titers between the younger and older subjects (Table 4). The geometric mean titers a month after the third vaccine dose were significantly greater ($P < .03$) on both schedules for younger than for older subjects. Also, the differences in geometric mean titers a month after the third dose were significantly greater ($P < .001$) for subjects in both age groups on schedule B than for those on schedule A (see Table 4).

TABLE 2.—*Adverse Effects Reported After the Hepatitis A Virus Vaccine*

Symptom	*Complaints After All Injections, %*
Pain at injection site	11
Nausea, vomiting	3
Headache	1
Fatigue	1
Dizziness	1
Backache	1
Flulike symptoms	1
Wheezing	1

Discussion

In this report, administering a formalin-inactivated hepatitis A vaccine to anti-HAV–negative hospital staff volunteers resulted in the production of antibodies to HAV in 100% of the persons vaccinated. When tested after the third dose of vaccine, subjects who received the 0-, 1-, and 12-month schedule had significantly higher titers of antibodies to HAV than those who received the 0-, 1-, and 2-month schedule. Also, our results using 720 ELISA units of inactivated hepatitis A vaccine at the 0-, 1-, and 12-month dosing schedule resulted in higher anti-HAV titers than those in a previous study using identical vaccine at varying doses administered at 0, 1, and 2 months.[3] Thus, our study shows that a time lag of longer than a month between the second and third dose of hepatitis A vaccine is required for higher antibody levels. For both of our vaccine dosing levels, younger subjects had higher HAV antibody levels than the older subjects. This last finding is similar to that reported with the hepatitis B vaccine in which the geometric mean titers of HBsAg after vaccination were noted to be lower in the older subjects.[9]

This hepatitis A vaccine was well tolerated, with transient injection site discomfort reported as the main side effect. Four subjects who had adverse reactions that may have been related to vaccine injection refused further vaccinations (see Table 3). Although possible, wheezing and rash have not been reported previously with this vaccine.

TABLE 3.—*Summary of 4 Persons With Adverse Reactions to the Initial Dose of Hepatitis A Virus Vaccine*

Subject	*Case Description*
1	A 56-year-old woman had wheezing after vaccination, which lasted 30 minutes; no treatment was required, and she recovered
2	After the first dose of vaccine, a 20-year-old man had an achy jaw, upset stomach, flulike symptoms, and fatigue that lasted 2 days
3	1 Day after vaccination, a 63-year-old woman had a flulike illness, malaise, and nausea that lasted 24 hours
4	5 Days after vaccination, a 74-year-old man noted the onset of a papular rash, tender scalp, painful finger pads, malaise, and abdominal discomfort; he was given diphenhydramine hydrochloride and prednisone with immediate recovery

We noted mild serum ALT elevations in 11 subjects. When remeasured during the follow-up period, the serum ALT values all had returned to normal. In the four persons who had more than one abnormal ALT value, the HBsAg test and the test of antibodies to the hepatitis C virus measured by a second-generation test were negative. Other studies on the use of HAV vaccine in healthy populations also reported slight but transient elevations of serum transaminase levels.[4,5] If a live attenuated HAV vaccine is used, it is conceivable that infection of hepatocytes may take place, but in the case of an inactivated vaccine preparation, other causes of serum aminotransferase elevation must be considered. In our subjects, the reasons for the ALT and AST elevations were not explained.

In two previous reports in which inactivated HAV vaccines were used, neutralizing antibodies were detected in 86% to 100% of subjects.[5,6] When the commercial HAVAB radioimmunoassay was used, one study reported

TABLE 4.—*Geometric Mean Titers of Antibodies to Hepatitis A Virus (HAV) in Recipients of Vaccine (given in IU/liter)*

	Subjects, No.	Month After Initial Dose of Vaccine				
		1	2	3	12	13
Schedule A						
≤40 yr	24	219*	446†‡	1,743§¶	806‡	839
>40 yr	25	190*	284†‡	826§¶	523‡	593
Schedule B						
≤40 yr	22	227*	590‡	514	351†	7,882§¶
>40 yr	30	269*	269‡	427	311†	4,279§¶

*Received second dose of HAV vaccine. †Received third dose of HAV vaccine. ‡$P < .20$. §$P < .03$. ¶$P < .001$.

only a 40% positivity, and none of the subjects had detectable anti-HAV immunoglobulin M by HAVAB-M.[5] In the other report, 31 of 32 (97%) had detectable anti-HAV by a radioimmunoassay technique that was different from HAVAB.[6] Two other studies using a single dose of attenuated live HAV vaccine showed that anti-HAV was detected in all subjects after vaccination, and neutralizing antibodies were also present in all of the vaccinees.[4,7] These preliminary reports indicate that both the live attenuated type and the killed type of HAV vaccines were immunogenic and well tolerated. In our study, the commercial HAVAB test was used as the initial screening test for anti-HAV. This test was different from the ELISA test that was done at SmithKline Biologicals in Belgium for detecting antibodies after HAV vaccination.[3] Although it is conceivable that some of the vaccinees may have had an initial positive titer by the ELISA test, none of them had an anamnestic response after the first dose of HAV vaccine, indicating that none of our subjects had had a previous exposure to the hepatitis A virus. Thus, the progressively rising antibody levels to HAV that were detected in our vaccinees were a result of the three HAV vaccine doses administered. In summary, the formalin-inactivated HAV vaccine that was used in this investigation produced higher antibody titers in subjects younger than 40 years, and the dosing schedule of 0, 1, and 12 months resulted in higher antibody levels than the 0-, 1-, and 2-month schedule. The HAV vaccine will be important in preventing acute hepatitis A and will contribute toward the eradication of this ubiquitous viral illness.

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Articles

Implications of an Audible Third Heart Sound in Evaluating Cardiac Function

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We prospectively compared auscultatory findings of third heart sounds with radionuclide ventriculographic analysis of systolic and diastolic function. Cardiac auscultation was done to detect an S_3 in patients referred for radionuclide ventriculographic analysis of ventricular function. Of 49 adult men with the diagnosis of chronic, nonvalvular heart failure who were referred for the evaluation of heart failure, 22 (45%) at the time of the ventriculography had an S_3 present on examination. For the entire study group, the radionuclide ventriculography-derived ejection fraction was 33% ± 19.5 (mean ± SD) with a range of 6% to 74%. The peak ejection rate was 2.05 ± 1.09 end-diastolic volume per second with a range of 0.30 to 4.56. The peak filling rate was 1.97 ± 1.07 end-diastolic volume per second with a range of 0.44 to 3.94, and the time to peak filling rate was 0.18 ± 0.11 per second with a range of 0.05 to 0.61. The presence of an S_3 was associated with a reduced ejection fraction and also with impaired diastolic function as determined by the peak filling rate. The sensitivity and specificity for the S_3 in detecting abnormal systolic function (ejection fraction < 50%) were 51% and 90%, respectively, with a positive predictive value of 95% and a negative predictive value of only 32%. For an ejection fraction of less than 30%, the S_3 had a sensitivity and specificity of 78% and 88%. The presence of an S_3 was highly predictive of an abnormal ejection fraction. The absence of an S_3, however, is not uncommon in patients with a mildly impaired ejection fraction.

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The diastolic sound that occurs during rapid ventricular filling, synchronous to the rapid descent of the ventricular pressure wave, is called the third heart sound (S_3).[1-4] The S_3 temporally follows ventricular relaxation and occurs simultaneously with rapid ventricular filling. The origins of the sound remain undefined. Classic explanations have included the following:

- Early diastolic effects of the ventricle on the chest wall,
- Overfilling of the failing ventricle with partial tensing of the support of the valvular structures, and
- Rapid pressure decompression of residual fluid in the ventricle in early diastole.

The intensity of an S_3 is increased by rapid early diastolic filling, such as in cases of elevated atrial pressure—as in mitral regurgitation.[5] The S_3 is also frequently noted in hyperdynamic states, such as anemia and thyrotoxicosis, and in patients with an arteriovenous fistula. The intensity of the S_3 also increases during inotropic therapy.[6] In practice, the presence of an S_3 is often used by primary clinicians to suggest the presence of congestive heart failure, but the overall accuracy of the S_3 as an indicator for systolic or diastolic dysfunction is largely unknown.

Because the S_3 occurs during rapid ventricular filling, we hypothesized that the presence of an S_3 would predict abnormalities in the measurements of ventricular filling as determined by radionuclide ventriculography. Similarly, because the S_3 occurs after systole is completed, we hypothesized that the presence of an S_3 would not closely correlate to abnormalities of systolic function determined by radionuclide ventriculography.

The purpose of our study was to assess the relationship between the third heart sound and systolic and diastolic dysfunction as determined by radionuclide angiography. We were specifically seeking to determine the accuracy and reliability of an S_3 for detecting cardiac dysfunction in a group of patients referred for the evaluation of congestive heart failure.

Patients and Methods

Our study included 49 patients referred to the nuclear medicine department (Department of Veterans Affairs, Hines, Illinois, Medical Center) for radionuclide ventriculography with the diagnosis of nonvalvular chronic heart failure. On the day of the radionuclide ventriculographic study, all patients were examined separately by the same two internists (R.P., D.B.) for the presence of an S_3 using

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ABBREVIATIONS USED IN TEXT

EDV = end-diastolic volume
PER = peak ejection rate
PFR = peak filling rate
TPER = time to peak ejection rate
TPFR = time to peak filling rate

the bell of a good-quality stethoscope placed over the point of maximal impulse. If an S_3 was not audible in the supine position, the patient was auscultated in the left lateral decubitus position. In the event of a disagreement, a third physician at the medical center (a cardiologist) was asked to examine the patient. The hospital's human studies committee waived requirements for informed consent.

Radionuclide ventriculographic studies were performed using a modified in vivo technique for labeling autologous erythrocytes with 25 mCi of technetium Tc 99m. A small-field gamma camera was used to obtain the images with gating at 32 frames per cycle using a buffered frame mode acquisition. The left anterior oblique view with a 10-degree caudal tilt was used for calculating all radionuclide ventriculography measurements. Counts of 6.5 million were obtained for each left anterior oblique view. Using an automated edge detection method, the cinematographic images were analyzed to generate a time-activity curve for determining the ejection fraction, peak ejection rate (PER), peak filling rate (PFR), time to peak filling rate (TPFR), and time to peak ejection rate (TPER). Diastolic pressures were not normalized for the RR interval.

The normal limits for PFR, TPFR, and PER were determined in the nuclear medicine laboratory using 35 subjects referred for multigated acquisition as part of a prechemotherapy assessment, who were found to have ejection fractions of greater than 50% and no evidence of infarction or hypertrophy on electrocardiography.

Data Analysis

The sensitivity, specificity, positive predictive value, and negative predictive value of an audible S_3 for predicting ejection fractions of less than 0.50 or 0.30, abnormal PFR (< 1.6 end-diastolic volume [EDV] per second), abnormal TPFR (> 0.360 seconds), and abnormal PER (< 2.3 EDV per second) were calculated. The student's t test was used to compare mean values of the ejection fraction, PER, PFR, and TPFR for patients with or without an S_3 (Table 1).

Results

All 49 patients enrolled in the study were men. Ages ranged from 49 to 74 years with a mean of 61.3 years. The mean age of patients with an audible S_3 was significantly less than those without an S_3 (56.6 versus 65.0 years). The mean ejection fraction of all patients referred was 33.1 ± 19.5 (mean ± SD). As a group, however, those patients with an audible S_3 had significantly lower ejection fractions compared with those without an S_3 (19.0 ± 13.3 versus 44.9 ± 16.6 [$P < .001$]). The PER for all referred patients was 2.05 ± 1.09 EDV per second, with a significantly slower PER for those patients with an S_3 than for those without an S_3 (1.37 ± 0.98 versus 2.35 ± 0.91 [$P < .001$]). The PFR among the patients with an S_3 was 1.50 ± 1.01 EDV per second, compared with 2.38 ± 1.01 for those without an S_3 ($P = .005$). The mean TPFR was significantly different for those with an S_3 versus those without (0.148 ± 0.086 second versus 0.215 ± 0.131 second [$P = .05$]) (see Table 1).

The sensitivity, specificity, positive predictive value, and negative predictive value of an audible S_3 for ejection fractions of less than 50% or less than 30%, an abnormal PER, an abnormal PFR, and an abnormal TPFR are given in Table 2. Ten patients had ejection fractions of more than 50%. Of the remaining 39 patients, 23 had ejection fractions of less than 30%. On examination, 21 patients had an audible S_3. Of these, 20 had ejection fractions of less than 50% (positive predictive value of 95%) and 18 patients had ejection fractions of less than 30%. Of the 28 patients who did not have an S_3 on physical examination, only 9 had a normal ejection fraction (negative predictive value of 32%), but 23 of these patients had ejection fractions of greater than 30% (negative predictive value of 82%).

The correlation between the peak ejection rate and the ejection fraction was calculated by least-square linear regression with $r = 0.89$, $P < .001$. Similarly, a correlation between the peak filling rate and the ejection fraction was documented with $r = 0.73$, $P < .001$.

Discussion

We undertook this study to examine the value of a third heart sound in predicting poor left ventricular perfor-

TABLE 1.—*Radionuclide Ventriculography (MUGA) Variables and Age Distribution in Patients With and Without a Third Heart Sound*

Variable	S_3 Present* Yes	No	P Value
Age, yr	56.5 ± 12.6	65 ± 9.2	<.05
Ejection fraction, %	19 ± 13.3	44.9 ± 16.6	<.001
Peak ejection rate, EDV/sec	1.37 ± 0.98	2.35 ± 0.91	<.001
Peak filling rate, EDV/sec	1.5 ± 1.01	2.381 ± 1.014	.005
Time to peak filling rate, sec	0.148 ± 0.086	0.215 ± 0.131	.05

EDV = end-diastolic volume, MUGA = multigated acquisition

*Values are mean ± SD.

TABLE 2.—*Sensitivity, Specificity, and Predictive Values for Ejection Fraction Indices in Patients With a Third Heart Sound*

	Sensitivity		Specificity		Positive Predictive Value		Negative Predictive Value	
Index	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
EF < 50%, n = 39	51	(33-67)	90	(56-100)	95	(76-100)	32	(16-52)
EF < 30%, n = 23	78	(56-92)	88	(70-98)	86	(64-97)	82	(63-94)
Abnormal PER	64	(44-81)	78	(56-92)	78	(56-92)	64	(44-81)
Abnormal PFR	61	(39-80)	73	(52-88)	66	(43-85)	68	(47-84)
Abnormal TPFR	0	(0-71)	54	(33-69)	0	(0-16)	89	(72-98)

CI = confidence interval, EF = ejection fraction, PER = peak ejection rate, PFR = peak filling rate, TPFR = time to peak filling rate

mance. The reliability of this finding as an indication of left ventricular dysfunction has not been carefully studied with modern diagnostic methods. The presence of an S_3 has traditionally been associated with poor ventricular systolic performance; however, we had expected that the S_3 might be more closely associated with abnormalities of the diastolic index because of its synchrony with diastole.

The third heart sound occurs early in diastole following mitral valve opening. Nonetheless, we found the presence of an S_3 to be more closely associated with abnormalities of ejection phase indices, such as the ejection fraction and peak ejection rate, than with the diastolic index of the peak filling rate. Comparing the percentage of patients with an S_3 in each multigated-acquisition-measurements group for normal versus abnormal indices showed that the presence of an S_3 was closely associated with an ejection fraction of less than 50%, less than 30%, and the peak ejection rate (χ^2, $P = .01$, $P < .001$, and $P = .001$, respectively). The association with the peak filling rate and the time to peak filling rate was not as strong, however (χ^2, $P = .025$ and $P = .08$, respectively).

The results with the greatest practical clinical importance are those that show the reliability of an S_3 for predicting cardiac dysfunction. The positive predictive value of an S_3 for identifying patients with an ejection fraction of less than 0.50 is excellent (95%, with a 95% confidence interval of 76% to 100%). The corresponding negative predictive value is only 32%, however, indicating that physicians cannot reliably exclude at least mild systolic dysfunction when an S_3 is not heard. The corresponding specificity and sensitivity are 90% and 51%, respectively, for identifying ejection fractions of less than 0.50. For detecting severely reduced ejection fractions of less than 0.30, the positive predictive value of an S_3 is still good at 86% and the negative predictive value, as expected, is much better at 82%. Therefore, in the absence of an audible third heart sound, a clinician can, with good confidence, exclude the presence of severe systolic dysfunction (defined as an ejection fraction of less than 30%). As a consequence of the excellent specificity and the high positive predictive value of an audible S_3 for identifying ejection fractions of less than 0.50, a clinician can be highly confident that systolic dysfunction is present when a third heart sound is heard. The sensitivity and negative predictive value of the S_3 are also high for patients with severe systolic dysfunction. Whereas predictive values can be criticized for their dependence on disease prevalence, these values are effectively used by clinicians in making medical decisions, although some estimation of disease likelihood (prevalence) is made before test results are obtained. It should be noted that there was roughly an even split in our population between patients with severe systolic dysfunction (23) and those without severe systolic dysfunction (26), although our population included a somewhat smaller number with normal systolic function (10).

Although the S_3 occurs in diastole, its association with the index of diastolic dysfunction, as determined by gated blood pool scanning, is modest. The presence of an S_3 can predict abnormal peak filling rates, with a positive predictive value of 66% and a specificity of 73%. The value of the presence of an S_3 in positively predicting abnormally delayed time to peak filling rate is 0% with a specificity of 54%. Therefore, although the presence of an S_3 appears to have some association with abnormally slow filling rates, it is not associated with a delayed time to peak filling rate.

The idea that the heart sound heard in early diastole may be associated closely with abnormalities of systole is intriguing. Early rapid ventricular filling occurs following the mitral valve opening. Despite the rapid influx of blood to the ventricle, pressure continues to decline. Indeed, 40% to 60% of the total ventricular volume is completed at or before the time that ventricular pressure reaches minimum. Because a notable amount of ventricular filling occurs early in the rapid filling phase and is thought to be simultaneous with the occurrence of an S_3, we thought that diastolic filling variables, determined by radionuclide ventriculography, would be intimately associated with auscultation findings of an S_3, which occurs simultaneously with this early rapid filling. Late ventricular filling and atrial kick-dependent ventricular filling are the late diastolic events. The contribution of ventricular filling (preload) that occurs during early diastole is dependent, in part, on the time course of ventricular relaxation and the atrioventricular pressure gradient. Thus, events that contribute to early rapid ventricular filling occur during isovolumic relaxation, before mitral valve opening. This, therefore, may link measurements of systolic events to auscultatory and measurable findings of diastole.

There is precedent in the basic physiology literature to consider early ventricular filling as a systolic event. Brutsaert and Rademakers have proposed that the traditional concepts of a well-defined end to ejection and discreet onset of diastole be abandoned.[7] Their concept of systole and diastole recognizes that the early filling reflects the rate and completeness of ventricular relaxation, both be-

fore and immediately following mitral valve opening. This concept then links late systolic events, through relaxation, to early filling.

Our study is limited by the use of an audible S_3, as opposed to the use of diagnostic phonocardiography. For practicing physicians, an auscultated S_3 is a more appropriate and relevant measure in terms of patient care. Furthermore, the use of radionuclide angiography to assess the derivative values of ventricular function is critically dependent on acquisition and edge-detection algorithms.[8] The diastolic measurements are also dependent on the mitral valvular function, atrioventricular pressure gradient, and perhaps the heart rate. Nonetheless, these findings provide insight into the pathogenesis of the clinically appreciable S_3 and give a good indication of the reliability and accuracy of the S_3 for predicting various degrees of cardiac systolic and diastolic dysfunction.

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Epitomes

Important Advances in Clinical Medicine

Allergy and Immunology

The Council on Scientific Affairs of the California Medical Association presents the following inventory of items of progress in allergy and immunology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome, and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, researchers, and scholars to stay abreast of these items of progress in allergy and immunology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Allergy and Immunology of the California Medical Association, and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
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Food-Induced Anaphylaxis

FOOD-INDUCED ANAPHYLAXIS is a rare but dramatic and potentially fatal condition that occurs in patients with hypersensitivity to a food. Nearly all patients with food-induced anaphylaxis have had previous adverse reaction(s) to the food at fault. Anaphylactic reactions to a food are almost always immunoglobulin (Ig) E-mediated, and because of this, patients usually will have a positive skin-prick test unless they have recently taken antihistaminic drugs or are in a refractory state, which may last as long as two weeks after an anaphylactic episode.

Although there is no particular age or sex predilection for food-induced anaphylaxis, nearly all persons with this disorder are highly atopic, and many have a history of asthma that requires β_2-agonists or a history of eczema or allergic rhinitis. They often have many food allergies. In about 85% of the patients, the anaphylactic event occurs away from home, where there is less control over constituents and trace contaminants in the food or drink ingested. The foods most commonly causing a reaction in adults, in descending order, are peanuts, tree nuts, milk, eggs, shellfish, other fish, and miscellaneous foods including cereal grains, celery, and fruits. In early childhood, cow's milk and soy proteins are major allergens. Patients usually are not aware that the offending food has been ingested. Two common characteristics in many patients who die of food-induced anaphylaxis are denial of the severity of their food allergy and a reliance on oral antihistaminics alone to treat their symptoms.

Three clinical patterns that have been observed are uniphasic, biphasic, and protracted. About half of the patients have a uniphasic pattern. In severe uniphasic reactions, symptoms usually begin one to five minutes after ingestion of the offending agent. A sensation of itching and tingling in the mouth is followed by tightness of the throat, nausea, vomiting, and urticaria, progressing within 30 minutes to dyspnea, cyanosis, arrhythmias, hypotension, and shock. About a quarter of food-induced anaphylactic episodes are biphasic, with early oral and abdominal symptoms followed by an asymptomatic period of one to two hours, after which severe respiratory symptoms, hypotension, and shock may occur. In another quarter of episodes, patients have protracted cardiorespiratory symptoms requiring vasopressor medications and ventilatory support for more than 24 hours. A special form of food-induced anaphylaxis may occur in conjunction with exercise. In these cases, neither ingestion of the food nor exercise will, by itself, cause anaphylaxis. The reaction occurs during or immediately following exercise, but only if the offending food is ingested within a few hours before exercise takes place.

In most instances, the initial immunologic reaction occurs when food antigen binds to IgE antibodies attached to high-affinity receptors on sensitized mast cells. These cells are activated, causing the release of a host of biologically potent chemical mediators including histamine, leukotrienes, prostaglandins, bradykinin, platelet-activating factor, and others. The result is increased vascular permeability, edema, bronchial smooth muscle contraction, and peripheral vasodilation. Although IgE-mediated reactions account for most food-induced anaphylaxis, nonimmunologic or anaphylactoid reactions have been known to occur.

Most patients with anaphylactic reactions to a food have positive skin-prick tests to that food. Immunoglobulin E antibody tests are advantageous if a patient has dermographism, if the patient will be seen only during the anaphylactic or postanaphylactic period, or if there has been recent therapy with antihistaminics, all of which can invalidate skin tests. Intradermal skin tests and oral challenge tests should be avoided because of the danger of severe systemic reactions.

Prevention is the management of choice for food-in-

duced anaphylaxis. Patients should be warned in an unequivocal but considerate manner that they are at an increased risk for anaphylaxis and that death could result if instructions are not conscientiously followed. All foods to which the patient is allergic should be identified by careful history, skin-prick tests, and IgE antibody assays. Patients and parents should be taught to read labels and interpret lists of ingredients on packaged foods. Epinephrine and antihistaminics should be available at all times and should be given at the earliest sign of food-induced anaphylaxis. Epinephrine kits are available by prescription and should be available at child care locales and schools. As with any severe episode of anaphylaxis, life support measures may become necessary.

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Treatment of Human Immunodeficiency Virus Disease

TREATMENT OPTIONS for the spectrum of human immunodeficiency virus (HIV) disease and its complications continue to evolve. A goal of HIV disease management is to enhance or restore immune function. Although this has proved to be elusive, ongoing research appears promising for both active immunotherapy with vaccines, cytokine therapy, and ex vivo cellular expansion and passive immunotherapy with anti-HIV immunoglobulin infusions. Interferon alfa, an immune modulator approved for use in HIV-infected patients with Kaposi's sarcoma, is also under intensive investigation as an antiretroviral agent in combination with zidovudine.

The immune system may have less to battle if common and opportunistic infections can be prevented. This requires vaccination and prophylaxis. Preventive therapies for opportunistic infections continue to be an essential element of HIV disease management and the focus of intense research. Current recommendations include prophylaxis of *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex, and the use of preventive vaccines. The vaccines advocated include influenza, pneumococcal, hepatitis B, and routine childhood vaccines. It is recommended that the influenza vaccine be given yearly in October or November. The pneumococcal polysaccharide vaccine is recommended for all HIV-seropositive patients per the guidelines of the Centers for Disease Control and Prevention (CDC). Revaccination should be considered for patients having received the vaccine more than six years ago. Hepatitis B vaccine is advocated for all HIV-seropositive patients who are not immune (demonstrating antibody to core or surface protein) and who remain at risk for the hepatitis B virus. Recommendations for tetanus, mumps, rubella, and measles vaccination are the same as for patients without HIV disease. For patients traveling abroad, the recommendations are also the same as for persons without HIV, except for live vaccines (yellow fever, live oral polio, and live oral typhoid), which remain strictly contraindicated for all immunocompromised patients.

Pneumocystis carinii pneumonia prophylaxis is currently advocated for HIV-seropositive patients (primary prophylaxis) who have $CD4^+$ counts of less than 200×10^6 per liter (200 per μl) and any patient who has had *P carinii* pneumonia previously (secondary prophylaxis). Additional new indications include patients with constitutional symptoms such as oral candidiasis or unexplained fever for more than two weeks, regardless of the $CD4^+$ count. Clinical trials indicate the use of the combination product of trimethoprim and sulfamethoxazole to be superior to that of aerosolized pentamidine for preventing recurrent *P carinii* pneumonia (secondary prophylaxis); recent reports from the Eighth International AIDS Conference suggest that treatment with trimethoprimsulfamethoxazole is superior for primary prophylaxis as well. The recommended dose is one double-strength tablet per day. Alternative regimens include aerosolized pentamidine or dapsone.

Prophylaxis studies are being carried out for cytomegalovirus, *Cryptococcus neoformans*, *Toxoplasma gondii*, and other common opportunistic pathogens, and recommendations can be expected in the near future.

Primary tuberculosis, especially multiple drug-resistant tuberculosis, is a growing concern. *Mycobacterium tuberculosis* may be readily transmitted by the aerosol route, particularly during the administration of aerosolized pentamidine or other respiratory therapies. Consequently, it is now imperative to identify patients with active tuberculosis and to treat them rapidly and effectively. Tuberculosis testing is indicated for all HIV-seropositive patients; likewise, HIV testing is indicated for all persons with *M tuberculosis*. Skin testing with intermediate-strength purified protein derivative (PPD) is considered positive if there is 5 mm of induration. Anergy may cause the test to be falsely negative; therefore, concurrent controls with *Candida albicans*, tetanus toxoid, or mumps should be placed. Patients with a positive PPD should receive isoniazid prophylaxis for 12 months.

Prophylaxis for *Mycobacterium avium-intracellulare* is indicated for HIV-seropositive patients with CDC-defined acquired immunodeficiency syndrome (AIDS), particularly those with $CD4^+$ counts of less than 100×10^6 per liter. *M avium-intracellulare* is a possibly life-threatening opportunistic infection seen commonly in patients with AIDS. Estimates indicate that 30% to 50% of patients may be diagnosed with *M avium-intracellulare* within three years after their diagnosis of AIDS. Recently, rifabutin was approved for the prophylaxis of the disease; it has been well tolerated in clinical trials at the recommended dose of 300 mg a day. *M avium-intracellulare*

prophylaxis must not be given to patients with active tuberculosis.

There is no evidence that rifabutin is effective as prophylaxis against *M tuberculosis*. Patients requiring prophylaxis against both *M tuberculosis* and *M avium-intracellulare* may be given isoniazid and rifabutin concurrently.

Problems with polypharmacy may arise with the prophylaxis and the treatment of multiple potential opportunistic infections; as a result of this therapy, however, HIV-infected patients can expect to increase not only the duration but the quality of their life.

Compassion, understanding, and a working knowledge of new and emerging treatment options are prerequisites for the optimal management of HIV disease, which should now be considered a chronic manageable condition.

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Treatment and Prevention of Milk Allergy

COW'S MILK ALLERGY is a notable clinical problem, affecting about 1% of all infants. The most clearly understood manifestations are immunoglobulin (Ig) E-mediated and include anaphylaxis, urticaria, eczema, rhinitis, and asthma. The mechanisms for milk-induced enterocolitis, the malabsorption syndrome, and colic are unknown. The major cow's milk proteins implicated in allergic disease are casein and the whey proteins, α-lactalbumin, β-lactoglobulin, bovine serum albumin, and bovine serum γ-globulin. β-Lactoglobulin is thought to be the most allergenic. The diagnosis of milk allergy is based on a careful history, the demonstration of IgE antibodies either by epicutaneous skin test or radioallergosorbent test, and elimination and challenge when this can be safely done. The gold standard, however, a double-blind, placebo-controlled challenge test, is used when the diagnosis is in doubt and is mandatory when a new hypoallergenic formula is being tried.

For more than 50 years, intact animal and vegetable proteins have been used as substitute nutritional sources in infants with milk allergy. Soy formulas, however, have been shown to provoke allergic reactions—although not usually anaphylaxis—in cow's milk-sensitive infants, and yet they continue to be considered hypoallergenic by the medical community.

Cow's milk hydrolysates have been used for more than 40 years, but only recently have they been studied carefully, since even these products have produced anaphylaxis in a highly allergic infant. Cow's milk hydrolysates are derived from casein (such as Nutramigen, Pregestimil, and Alimentum) or whey (such as Good Start and Alfare, which is not available in the United States). These preparations are produced by exposing intact cow's milk protein to proteolytic enzymes, heat, and ultrafiltration. Preclinical evaluation has included physiochemical and immunologic testing to determine their antigenicity. Allergenicity has been assessed by the guinea pig anaphylaxis model and such in vitro analyses as the enzyme-linked immunosorbent assay (ELISA) or radioimmunoassay inhibition. For example, extensively hydrolyzed casein when analyzed by ELISA inhibition shows a decrease in allergenicity of more than 99%. The upper limits of tolerance are unknown, however, and may vary among infants.

Preclinical tests cannot predict with certainty that infants with cow's milk allergy will not react adversely to a hypoallergenic formula. Thus, labeling an infant formula as hypoallergenic requires careful clinical testing. It should be recognized that all formulas will produce reactions in some infants. All new hypoallergenic formulas must first be tested for their ability to promote normal growth and maintain a normal nutritional state. Thereafter, a double-blind, placebo-controlled challenge followed by an open challenge is required for formulas intended for infants with cow's milk allergy. The Committee on Nutrition of the American Academy of Pediatrics advises that for a formula to be labeled hypoallergenic, it should be tolerated by 90% of milk-allergic infants. The only formulas that currently have been shown to fulfill these criteria are Nutramigen, Pregestimil, and possibly Alimentum. These, therefore, are appropriate for use in a highly milk-sensitive infant.

Hypoallergenic does not mean nonallergenic, and, as indicated, anaphylaxis has been reported even with the formulas with known tolerance. To deal with this possibility, in this population it would be prudent to give the first dose in a setting where resuscitation can be initiated. Skin testing with these formulas might also prove helpful in this regard because a negative skin test is usually highly predictive, whereas a positive response is associated with a reaction in 30% to 40% of cases. Nonetheless, the proof is in the eating. Whether soy-based formulas would be useful in a highly milk-allergic infant is controversial at best. Faced with a highly milk-sensitive infant, most physicians recommend giving a casein hydrolysate at least for the first year and then reassessing the allergic status. A soy formula could be tried only if cost prohibits the use of a casein hydrolysate.

To prevent milk allergy, several studies have suggested that the mothers of these infants breast-feed and limit their intake of cow's milk; Nutramigen can be used as a supplement or alone. Recent studies also suggest that partially hydrolyzed preparations such as Good Start, but not soy-based formulas, may be effective as a preventive formula. These preventive measures should be continued for the first 6 to 12 months of life to be effective for children with a family history of food allergies.

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Exercise-Induced Asthma and Anaphylaxis

ALTHOUGH EXERCISE is a salutary activity for many people, for others it may provoke anaphylaxis or asthma. Exercise-induced asthma and exercise-induced anaphylaxis rarely occur in the same person and are thus considered separate disorders. The common factor is the form of exercise, which is almost invariably intense running for relatively short periods.

Exercise-induced asthma is defined as a transitory increase in airway resistance that follows vigorous exercise. It can be reproduced in the laboratory in about 80% of patients with asthma who exercise at 80% to 90% of their predicted maximal working capacity for six to eight minutes while breathing room air. The severity cannot be predicted by the resting level of lung function. Even persons with normal lung function can suffer severe asthma within minutes of completing exercise. Inhalation of a β-adrenergic aerosol or cromolyn sodium before exercise will prevent the occurrence in 90% of people with this reaction. The rest require either larger than usual doses or a combination of drugs for relief.

Proposed mechanisms for airway narrowing include the release of mast cell mediators such as histamine, the stimulation of vagal afferent pathways, and reactive local hyperemia and edema initiated not by an immunologic response but by abnormal water loss in the airways. Water loss results from a combination of temperature drop in the bronchial mucosa and hyperosmolarity of the periciliary fluid. Exercise-induced asthma has been prevented by having a patient inhale warmed or moist air during exercise.

Exercise-induced anaphylaxis can develop in persons without a history of asthma or even any allergic condition, although about half appear to be atopic. The prevalence is unknown, but one center has seen 500 cases over a 17-year period. Patients typically have a sensation of cutaneous warmth and pruritus initially, followed rapidly by generalized erythema, urticaria, hypotension, and upper respiratory tract obstruction during physical activity. Asthma rarely occurs. Although the reactions appear life-threatening and may require medical therapy for anaphylaxis, deaths have not been reported. Most patients are adolescents or younger adults, but the condition has been reported in a 4-year-old child.

Exercise-induced anaphylaxis may require another factor, food ingestion, with the physical activity. Anaphylaxis develops in some patients only in association with either a meal followed by exercise or eating a specific food for which they have immunoglobulin E antibodies. Strangely enough, either factor alone in this group with food-dependent, exercise-induced anaphylaxis will not provoke a generalized reaction. In addition, a familial tendency has been found in some cases.

A common mechanism has not been found for these diverse forms of exercise-induced anaphylaxis. A release of mediators such as histamine has occurred in only about half of the patients studied. Some with food dependency may have exaggerated blood volume shifts from the skeletal muscle circulation to the splanchnic vasculature during food digestion; others have demonstrable autonomic nervous system dysfunctions. Shared leukocyte antigen haplotypes have been found in the familial form.

Treatment may be defined as active or preventive. Active treatment is identical to the treatment of any type of anaphylaxis. Prevention involves restriction or changing the form of exercise and, in the food-dependent type, permitting exercise only before food intake. Pretreatment with histamine-1 antagonists or gradual increments of exercise has not proved uniformly effective. Exercise-induced asthma and anaphylaxis can be readily diagnosed and ameliorated by preventive meaures.

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Antihistamines and the Heart

THE TOXICITIES OF classic, first-generation histamine-1–receptor antagonist antihistamines have produced sedation, decreased mental alertness, and anticholinergic side effects. Beyond scattered reports of palpitations or hypotension in antihistamine overdosage, few serious adverse cardiovascular reactions have been described with the use of these agents.

With the development of second-generation, nonsedating H_1-receptor blockers, the spectrum of side effects has changed. Terfenadine, a relatively short-acting antihistamine that is extensively metabolized by the hepatic cytochrome P-450 system, induces a small increase in the corrected QT interval on electrocardiography, even at recommended dosages. This electrocardiographic change is rarely clinically important. When terfenadine is administered to patients with impaired hepatic function or given simultaneously with the macrolide antibiotics erythromycin or troleandomycin or with the imidazole antifungals ketoconazole or itraconazole, the QT interval may be more dramatically prolonged. This has resulted in serious ventricular tachyarrhythmias (including torsades de pointes and ventricular fibrillation) and death. These agents appear to alter terfenadine pharmacokinetics and may cause the accumulation of terfenadine in certain patients.

Clarithromycin and azithromycin, newer macrolide antibiotics with minimal effects on hepatic cytochrome P-450, have not been evaluated for their interactions with terfenadine. The possible drug interactions between fluconazole and terfenadine have not yet been characterized. The concomitant administration of these agents with terfenadine is not recommended until more data are available. Other clinical conditions that alone may prolong the QT interval and possibly increase the likelihood of terfenadine cardiotoxicity include hypokalemia, hypomagnesemia, hypocalcemia, and the congenital QT syndrome.

Astemizole, a longer-acting nonsedating antihistamine, has been reported to cause a wide spectrum of cardiac dysrhythmias in patients with acute overdose but rarely at recommended dosages. In addition to torsades de pointes and other ventricular tachyarrhythmias with prolonged QTc interval, first- and second-degree atrioventricular blocks and bundle branch blocks have been described, the last particularly in children. Because of the long half-life of astemizole metabolites, several days of cardiac monitoring and supportive therapy are recommended in patients with overdose with this agent.

Because of more limited experience with two other second-generation antihistamines soon to be available in the United States, cetirizine and loratidine, the spectrum of cardiac toxicity with these agents is less clear. Cetirizine is excreted largely unchanged in the urine, and patients with impaired renal function could have prolonged half-lifes for this drug. Loratidine, like astemizole and terfenadine, is metabolized by the liver. In any case, careful consideration to possible drug interactions and long-term clinical conditions should be given before prescribing second-generation antihistamines.

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Vocal Cord Dysfunction Presenting as Asthma

WHEEZING OCCURS IN various organic lung diseases as a result of reversible or irreversible airway narrowing, localized endobronchial disease (such as tumor or sarcoidosis), and diffuse or localized lung disease (such as pulmonary edema, lymphangitic disease, or pulmonary embolism). Vocal cord dysfunction, a recently described syndrome that presents as asthma, is an uncommon but important asthma impersonator that should be included in every physician's differential diagnosis of asthma.

The pathophysiologic mechanism involved in vocal cord dysfunction is a dysfunction of the larynx in which the vocal cords are inappropriately adducted during inspiration, expiration, or both. The sound produced can be similar to asthmatic wheezing, and patients may be mistakenly diagnosed and treated for asthma. Missing this diagnosis has serious consequences, for many patients have received tracheotomies or been aggressively treated for asthma with systemic corticosteroids, producing iatrogenic Cushing's syndrome.

The clinical presentation is often dramatic, with a frightened patient reporting to an emergency department or physician's office with one of many attacks of profound wheezing and dyspnea. Patients are typically young women between the ages of 20 and 40. The syndrome has recently been reported in children as well. On examination, there are inspiratory and expiratory wheezes loudest over the larynx and less well transmitted to the chest wall. Arterial blood gas values are usually normal, as opposed to the hypoxemia seen in acute asthma, and pulmonary function studies show pronounced variability in spirometric test results. Laryngoscopy during wheezing shows almost complete adduction of the vocal cords, with the glottis reduced to a small posterior diamond-shaped opening. This finding and the wheezing it produces can be reversed by asking the patient to cough or breathe in a panting manner. If seen when an attack is not occurring, the patient will often report that the wheezing comes from the throat and not the chest.

Because true asthma and vocal cord dysfunction can coexist, the use of a methacholine challenge test to evaluate a patient's bronchial hyperresponsiveness should be done in most patients. A flow-volume loop characteristic of extrathoracic airways obstruction can be helpful.

The cause of the condition is not clear, but a hypothesis is that "suggestion" mediated by the vagus nerve may alter the laryngeal tone and lower the threshold for stimuli to produce vocal cord spasm. Recently there have been several reports of cases of vocal cord dysfunction associated with gastroesophageal reflux, which reversed with treatment of the reflux.

Vocal cord dysfunction presenting as asthma can have a psychological basis. The operative mechanisms that come into play include conversion reactions associated with a variety of conditions, such as depression, a passive-dependent personality, and somatization disorder. These patients do not knowingly control their illness for secondary gain, and therefore it is not considered malingering. Therapy consists of a multidisciplinary approach including the physician, psychiatrist, and speech therapist. The physician's role is to inform the patient of the findings, especially the absence of diseases such as asthma, and to explain the nature of the condition. Patients often express a positive reaction to the initial explanation, and such a reaction often implies a good prognosis.

It must be recalled that vocal cord dysfunction and true asthma may coexist; therefore, in an acute attack, the patient should be treated for asthma unless there is absolute proof that asthma is not the cause of the symptoms.

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Sinusitis

SINUSITIS OFTEN EVADES RECOGNITION because of its protean and sometimes elusive clinical manifestations and because of the relative inaccessibility of the paranasal sinuses to direct visualization. Interest in sinus disease has been renewed by an increased awareness of its prevalence, possible ramifications (such as refractory asthma), and possible complications (such as intraorbital or intracranial extension). Recent progress toward understanding the cause and pathophysiology of sinusitis has been accompanied by important advances in diagnostic imaging and in medical and surgical therapy.

Recently it has been established that most sinus disease in adults and children involves the maxillary and anterior ethmoidal sinuses, both sets of which are present at birth and, along with the frontal sinuses, drain into the middle meatus. Disease of the sphenoidal and posterior ethmoidal sinuses, which drain through the superior meatus, and of the frontal sinuses is less common, but diagnostic sinus imaging always should include the frontal sinuses in patients older than 3 years and frontal plus sphenoidal sinuses in those older than 8 years.

New evidence from computed tomographic (CT) studies underscores the importance of ostial occlusion in the cause of sinusitis. This is especially apparent in the predisposition to ethmoid sinusitis, where even minimal mucosal edema, mucociliary stasis, or anatomic obstruction threatens the patency of the 1 to 2 mm in diameter ethmoidal air-cell ostia. Moreover, disease involving the anterior ethmoidal bullae and maxillary outflow tract (collectively called the ostiomeatal complex) predisposes to disease of the ipsilateral frontal, ethmoidal, and maxillary sinuses by obstructing their common drainage pathway through the middle meatus.

Acute sinusitis is most frequently a complication of upper respiratory tract infection. Allergy and, less so, irritant exposure (cigarette smoke), immunodeficiency, and mechanical obstruction (polyp, tumor, granuloma, adenoidal hypertrophy, foreign body, and septal deviation) underlie most instances of recurrent acute and chronic sinusitis. An important but less common occurrence is that sinusitis may be the first sign of systemic diseases such as Wegener's granulomatosis or diseases associated with mucus stasis, such as cystic fibrosis and mucociliary dyskinesia syndromes. Sinusitis should be suspected when signs and symptoms of upper respiratory tract infection persist longer than seven to ten days. The most common signs are cough, nasal discharge, fetor oris, periorbital swelling, and fever, with symptoms of headache, facial pain, odontalgia, and hyposmia reported by verbal children and adults. A sizable proportion of adults and children (40% to 75%) with asthma present with an often recalcitrant asthmatic exacerbation in association with sinusitis. In most patients, the resolution of sinusitis is accompanied by substantial lessening of asthma and a consequent reduction in the need for bronchodilator and corticosteroid use.

Flexible fiberoptic rhinoscopy, done in cooperative older children and in adults after the topical application of a vasoconstrictor and anesthetic, has permitted direct visualization of intranasal anatomy inaccessible to anterior rhinoscopy. The efflux of mucopurulent secretions from the middle meatus is a reliable indicator of acute sinusitis. Transillumination is less helpful because near-complete unilateral opacification is required to confirm the diagnosis. Similarly, nasal cytologic examination is relatively nonspecific. Coronal CT scanning is superseding radiography as the diagnostic imaging modality of choice and provides an excellent demonstration of bony landmarks and obstructing lesions of the ostiomeatal complex. Magnetic resonance imaging, while not producing satisfactory resolution of bony detail, is superior to CT in distinguishing soft-tissue characteristics. Ultrasonography has fallen into general disfavor because of its low sensitivity and specificity. Recent studies record as much as a 75% discordance rate between plain films and coronal CT, with conventional radiography substantially underestimating both the presence and extent of sinus disease. In many institutions, the cost of a limited coronal sinus CT study approximates that of a plain film sinus series. Because many cases of sinusitis can be diagnosed and treated on the basis of clinical suspicion alone, it is increasingly recommended that CT scanning as the sole imaging study be reserved for clinically suspected sinusitis that is refractory to medical management.

Culture of sinus aspirates obtained by transnasal maxillary antral puncture is far more predictive of actual intrasinus infection than nasal or nasopharyngeal cultures, but is impractical in routine clinical settings. A rational selection of empiric antimicrobial therapy may be guided by recent studies. *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* account for most cases of acute and chronic uncomplicated sinusitis in children and adults. α-Hemolytic streptococci and *Staphylococcus aureus* are identified occasionally in cases of long-standing or severe disease. Whereas anaerobes are rarer causes of sinusitis in children, *Bacteroides* species, almost half of which are β-lactamase–producing, and anaerobic cocci may cause most cases of chronic sinusitis in adults. In areas where the prevalence of β-lactamase–producing pathogens is low, acute sinusitis is appropriately treated with amoxicillin for three to four weeks.

Should clinical improvement not occur within 48 hours of starting first-line antibiotic therapy, a β-lactamase–resistant agent should be substituted. These include the combinations of amoxicillin and clavulanate potassium, erythromycin ethylsuccinate and sulfisoxazole, cefaclor (which is inactivated by β-lactamases of most *M catarrhalis* and *H influenzae*), trimethoprim and sul-

famethoxazole, cefuroxime, and cefixime (which has little activity against *S pneumoniae* and virtually none against *S aureus*).

Fungal (such as *Aspergillus fumigatus*) sinusitis is recognized increasingly in immunocompetent as well as immunocompromised patients. Invasive disease usually requires debridement and systemic antifungal drugs. Allergic fungal sinusitis is usually treated by debridement, systemic corticosteroids, and occasionally by systemic antifungal drugs.

Adjunctive treatment of sinusitis has not been evaluated by well-controlled studies. Many authorities favor nasal saline lavage and topical corticosteroid spray, such as beclomethasone dipropionate or flunisolide, in recurrent or chronic sinusitis, with the view that such low-risk therapy may aid sinus ventilation and mucociliary clearance by reducing nasal mucosal inflammation. Decongestants administered orally (pseudoephedrine hydrochloride, phenylpropanolamine hydrochloride) or topically (oxymetazoline hydrochloride, phenylephrine hydrochloride) may transiently lessen symptoms but also may inspissate secretions and reduce ciliary function, effects that may be counteracted by nasal saline lavage or mucoevacuants (such as guaifenesin). The anticholinergic properties of older-generation antihistamines likewise may dehydrate secretions and thus should be avoided in favor of newer-generation agents—that is, terfenadine, astemizole, and loratadine—but only when allergy is a suspected factor. Recently developed endoscopic sinus surgery for refractory chronic sinusitis may result in dramatic therapeutic success, largely because of its effectiveness in restoring natural drainage to the ostiomeatal complex with minimal disruption of sinus mucosa.

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Topical Nasal Steroids for Allergic Rhinitis

TOPICAL CORTICOSTEROIDS are currently the most potent medications available for the treatment of allergic rhinitis. Intranasal preparations eliminate the systemic side effects and equal or exceed the efficacy of their oral counterparts. The therapeutic effect produced is not completely understood but is thought to involve the inhibition of allergen-induced mediator release, the reduction of mast cell, basophil, and eosinophil accumulation on the nasal mucosal surface, and the inhibition of prostaglandin and leukotriene generation. Intranasal corticosteroid therapy has been shown to inhibit both the early and late inflammatory responses after allergen challenge.

Corticosteroids are highly effective in treating both seasonal and perennial allergic rhinitis. The control of nasal symptoms is achieved in at least 75% of patients, with comparable results in children and adults. Corticosteroid administration lessens all symptoms of allergic rhinitis including itching, sneezing, rhinorrhea, and blockage, and in some instances relieves eye symptoms. Corticosteroids have also been found to be useful in other rhinitis conditions, including nonallergic rhinitis with eosinophilia, nasal polyposis, rhinitis medicamentosa, and, in some patients, vasomotor rhinitis.

The potency of corticosteroids exceeds that of antihistamines, decongestants, and cromolyn sodium. This class of medication works best on a continual versus an as-needed basis. The relief of symptoms usually begins within two to three days of initiating therapy; a maximum response may require two to three weeks for some patients. Initially reserved as a second-line agent, the role of intranasally given steroids is changing. In the past, antihistamines, with or without decongestants, have been recommended as first-line therapy, but corticosteroids are increasingly being used as an initial drug for chronic allergic rhinitis. For those patients with substantial rhinitis or with persistent eye complaints, oral antihistamines or decongestants are usually necessary to complement intranasal steroid therapy. Therapy should be continued throughout the expected season for hay fever and may be required on a long-term basis for perennial allergic rhinitis.

Three synthetic corticosteroids, beclomethasone dipropionate, flunisolide, and triamcinolone, are available for the topical treatment of rhinitis. The anti-inflammatory activities of these preparations are in the range of 1,000 to 5,000 times greater than that of hydrocortisone. Most comparison studies of these different agents have yielded results suggesting that all appear to be similarly efficacious. Although initial recommendations with beclomethasone and flunisolide were that these drugs be administered four times a day, there is no evidence that anything is gained by dosage regimens more complicated than twice a day. For beclomethasone and flunisolide, the recommended adult starting dose is one to two sprays in each nostril twice a day. Triamcinolone, the newest available intranasal corticosteroid, has been marketed as a once-a-day medication, and, indeed, studies using one to two sprays in each nostril once a day have shown it to be efficacious. In many patients, once-a-day dosing is often possible with beclomethasone and flunisolide, particularly after the patient has obtained control of rhinitis on the higher initial twice-a-day starting dose. The dose of the nasal steroid should be adjusted based on the clinical response, with the goal to use the lowest dose that provides efficacy.

The major difference in the various available corticosteroid preparations has more to do with the vehicle and delivery system than with their potency. These differences primarily predict the variability of acceptance of the different preparations. Flunisolide is most commonly associated with burning and stinging, related to the propy-

lene glycol in the vehicle and its associated low pH rather than from the drug itself. A new formulation with less propylene glycol is in development and may eliminate this problem. Beclomethasone is available as a freon-propelled metered-dose unit (Beconase, Vancenase) and an aqueous formulation (Beconase AQ, Vancenase AQ). The pump sprays that use the aqueous formulation appear to provide better distribution of the drug compared with the aerosol, although few studies have directly compared the mode of delivery, and clearly both preparations relieve symptoms relative to placebo. Certain patients prefer the freon-propelled aerosol delivery system because there is less medication run-off than with an aqueous formulation. Triamcinolone (Nasacort) is available as a freon-propelled aerosol with a slightly different nasal adaptor delivery device from the aerosol version of beclomethasone.

Local nasal irritation is the major side effect of intranasal corticosteroids. This problem is usually not important and rarely prevents a patient from complying with the regimen. About 1% to 2% of patients will have a bloody discharge, and septal perforations have been rarely detected. Biopsies of the nasal mucosa of patients who have received beclomethasone continuously for at least five years have shown no signs of atrophy or metaplasia. Systemic side effects have not been detected in clinical trials using the three synthetic steroid preparations, although if carefully looked for, systemic absorption and even some mild effects on the hypothalamic pituitary-adrenal axis can be measured. Recent data from studies of corticosteroid therapy for asthma suggest that long-term inhaled corticosteroid therapy may be associated with adrenal atrophy, decreased bone formation, impaired growth, and cataract formation, but all of these findings are the subject of dispute. The patient at greatest risk for complications is anyone, particularly a child, being treated with inhaled steroids for both asthma and rhinitis and therefore receiving an overall considerable dose of inhaled steroid, possibly leading to sizable systemic absorption and resulting steroid side effects. Although the risks of systemic effects accruing from the long-term use of intermediate or high doses of corticosteroids need further study, it can be argued that, given the available information, corticosteroids at standard doses are a valuable tool in the management of several types of rhinitis with an acceptable risk-to-benefit ratio.

New corticosteroid preparations on the horizon include budesonide and fluticasone propionate. Both have a high ratio of topical to systemic activity over a wide dose range and appear at least as effective as beclomethasone and flunisolide in the treatment of allergic rhinitis, offering a therapeutic alternative to currently available agents. Because chlorofluorohydrocarbons will be banned in the near future, powder-type corticosteroids are being studied and may represent a new delivery system.

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Latex Allergy

LATEX IS THE MILKY SAP obtained from numerous plants, predominantly the rubber tree (*Hevea brasiliensis*), and is used in the manufacture of natural rubber products for both medical and nonmedical uses. Products containing natural rubber include surgical, examination, and cleaning gloves, condoms, balloons, catheters, rubber bands, and elastic adhesives used in dentistry. Synthetic rubber products (derived from petroleum and alcohol) are increasingly being used and do not contain latex.

Two types of allergic reactions to latex-containing products have been described. Contact dermatitis (T cell-mediated, type IV hypersensitivity) from exposure to rubber products, especially gloves, has been recognized for decades. This immunologic reaction is not against latex antigens but to sensitizing chemicals added during the manufacturing process, such as mercaptobenzothiazole or tetramethylthiuram. This reaction can be determined by patch testing for the relevant additives.

Since 1979, there have been an increasing number of reports in the medical literature of immunoglobulin (Ig) E-mediated allergic reactions (immediate, type I hypersensitivity) to latex-containing products. Clinical reactions have included local contact urticaria, systemic urticaria, rhinoconjunctivitis, asthma, or anaphylaxis. Most dramatic have been reports of intraoperative anaphylaxis from exposure to surgical gloves and other latex-containing products and anaphylactic reactions from rubber-tipped enema catheters. Exposure to latex allergen has usually been at mucosal surfaces but can also be from other cutaneous, percutaneous, and parenteral transmission. Aerosol transmission has also been described and is postulated to be caused by latex allergen adhering to cornstarch released into the air with the manipulation of rubber gloves.

The prevalence of IgE-mediated latex allergy in the general population is not known but appears to be low, less than 1%. Allergic reactions to latex are more often seen in atopic persons, and those with prolonged or repeated exposure to latex products are at increased risk. Between 18% and 28% of children with myelodysplasia have a history of acute allergic reactions to rubber products. A serologic survey of similar patients revealed 34% to have rubber-specific IgE by radioallergosorbent test (RAST). Children with congenital urologic abnormalities also have an increased risk of IgE-mediated latex allergy; in both of these groups, the allergy presumably is from frequent urinary bladder or bowel catheterization and multiple surgical procedures. Those with occupational exposure to rubber products, such as health care professionals or rubber-industry workers, also are at an increased risk related to the amount of exposure. In a study of

employees of a university hospital in Finland, 1 of 130 (0.8%) workers not involved in health care were found to have immediate hypersensitivity to latex, whereas 2.9% of all physicians and nurses in the hospital had IgE-mediated sensitivity and 5.6% of nurses and 7.4% of physicians in the operating room were sensitive. Another study has shown about 11% of surgical nurses to have latex allergy.

The evaluation of patients for IgE-mediated latex allergy is done by either epicutaneous testing or in vitro testing. The largest study done in more than 900 health care professionals showed 100% sensitivity and 99% specificity of epicutaneous testing. Anaphylactic reactions to skin testing have been reported, though rarely. There are no US Food and Drug Administration-approved extracts available in the United States, although skin testing can be done with natural latex or with rubber products such as gloves. The amount of allergen in latex products varies with different manufacturers and even different lots, so they are an unreliable testing source. There is a commercial extract for skin testing available in Canada. In vitro tests are commercially available in the United States, but most studies have shown RAST testing to be less sensitive than skin testing. The specific latex allergens have been incompletely characterized to date.

We need to be able to identify patients at risk for latex allergy before surgical, medical, radiologic, or dental procedures. Rubber-allergic health care professionals also need to be able to work in a latex-free environment. Because no test is currently accepted for availability, reliability, and safety, a history of a possible allergic reaction is the only factor available in identifying at-risk patients. Recommendations have been to test any high-risk patients by skin testing, if available, or by in vitro testing. Patients with evidence of IgE-mediated sensitivity to latex or any history of previous latex allergic reaction should strictly avoid all latex products. The predictive value of a positive skin test or in vitro test in patients with no history of latex allergy is unknown, and large prospective studies are needed before further recommendations can be made. There have been no controlled trials done, but prophylactic premedication with histamine-1 and -2 antihistamines and parenteral steroids (similar to recommendations for radiocontrast media reactions) can be tried in patients known to be sensitive. There have been reports of the failure of premedication in patients with parenteral infusion of latex proteins. The avoidance of latex products is preferable.

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Alerts, Notices, and Case Reports

Tularemia From Domestic Cats

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TULAREMIA IS A ZOONOSIS of considerable complexity, with greater than 100 species of wild mammals, several species of birds, fish, and amphibians, and more than 50 species of blood-sucking arthropods (including ticks, fleas, and deerflies) serving as natural hosts.[1-5] Although the west south-central region of the United States—Arkansas, Louisiana, Oklahoma, and Texas—accounts for about a third of the cases reported to the Centers for Disease Control and Prevention, human tularemia has been reported from every state except Hawaii.[6] Humans generally acquire tularemia by direct contact with infected wild mammals or from arthropod bites, and the diagnosis of tularemia is traditionally considered in a hunter or trapper who presents with an acute febrile illness. Domestic animals, including dogs and cats, may also serve as vectors of tularemia.[8-18]

Two cases of septicemic tularemia recently occurred in the Fairbanks, Alaska, region following contact with domestic cats infected with *Francisella tularensis*. Tularemia was not suspected initially in either case because of the absence of either lymphadenopathy or a typical clinical history involving contact with wild mammals. In both cases, awareness of the clinical presentation of typhoidal tularemia and recognition of the potential for transmission of tularemia by domestic pets guided appropriate empiric antibiotic treatment before serologic confirmation.

Report of Cases

Patient 1

The patient, a 44-year-old man, was admitted to Fairbanks Memorial Hospital with a three-week history of a severe febrile illness unresponsive to treatment with oral cefadroxil. Three and a half weeks before admission, he sustained a cat bite to his right index finger while transporting his 14-year-old house cat to a veterinarian for management of a febrile illness diagnosed as an unspecified bacterial infection. The cat was empirically treated with intramuscular kanamycin sulfate and oral amoxicillin with complete resolution of symptoms. Three days after the cat bite, the patient had hectic spiking fevers to 40.5°C (105°F), chills, localized inflammation of the right index finger, headache, progressive weakness and malaise, nausea, abdominal pain, diarrhea, and anorexia associated with a 13.6-kg (30-lb) weight loss over the ensuing three-week period. He did not have a history of lymphadenopathy, respiratory symptoms, illicit drug use, alcohol abuse, recent travel outside the Fairbanks region, hunting, or trapping.

On physical examination on admission, there was a 1-cm nontender, ulcerated, erythematous skin nodule on the right index finger and relative bradycardia (heart rate 80 to 85 beats per minute in the presence of fever to 41°C). Otherwise, the physical findings were essentially normal. Admission laboratory studies revealed a hematocrit of 0.35, a leukocyte count of 10.5×10^9 per liter (10,500 per μl), aspartate aminotransferase 150 U per liter (normal, 0 to 35), alanine aminotransferase 154 U per liter (normal, 0 to 35), γ-glutamyltransferase 142 U per liter (normal, 0 to 30), alkaline phosphatase 190 U per liter (normal, 30 to 120), and total bilirubin 24 μmol per liter (1.4 mg per dl). A Monospot slide test was negative for infectious mononucleosis, and serologic tests were negative for rheumatoid factor and rapid plasma reagin. Cultures of blood and an aspirate of the right index finger yielded no bacterial growth.

The possibility of tularemia was suspected clinically, and empiric therapy with tetracycline, 500 mg orally every six hours, was initiated, leading to prompt defervescence and a resolution of symptoms within 48 hours. Oral tetracycline therapy was continued following hospital discharge to complete a four-week course of treatment. No relapse in symptoms occurred following the completion of therapy. A tularemia agglutination titer obtained on hospital admission was positive at 1:160; a titer done two months later during convalescence was positive at 1:320. A tularemia titer obtained from the cat a month after its febrile illness resolved was positive at 1:80. Serologic tests were negative for brucellosis in both cases.

Patient 2

The patient, a 42-year-old male veterinarian, presented for medical evaluation following the abrupt development of hectic fevers to 40.5°C (105°F) and chills associated with severe headache, photophobia, depression, generalized weakness, malaise, myalgias, arthralgias, abdominal pain, and diarrhea. Before the evaluation, the patient treated himself with oral cephalexin for a week without improvement. Sinusitis was suspected clinically, but prescribed treatment with oral amoxicillin for a week provided no benefit. The patient was admitted to Fairbanks Memorial Hospital two weeks into the course of his illness after a documented 9-kg (20-lb) weight loss. He did not have a recent history of skin lesions, adenopathy, respiratory symptoms, illicit drug use, alcohol abuse, hunting, travel outside the Fairbanks area, animal bites, or exposure to brucellosis, but he had treated several birds with psittacosis and several cats with tularemia during the

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two-month period before his illness began. None of his family members or co-workers at the veterinary practice had experienced a similar illness.

On physical examination there was a relative bradycardia: heart rate 75 to 85 beats per minute in the presence of temperatures of 39.5°C to 41.0°C (103°F to 106°F). An initial laboratory evaluation revealed normal electrolyte values, a hematocrit of 0.32, a leukocyte count of 9.6×10^9 per liter (9,600 per μl) with a normal differential cell count, an erythrocyte sedimentation rate of 43 mm per hour, normal liver function test values, and normal urinalysis. A Monospot slide test was negative for mononucleosis, and tests for antinuclear antibody and rheumatoid factor were negative. Three sets of blood specimens for culture yielded no bacterial growth. Chest x-ray and paranasal sinus films were within normal limits. Computed tomography of the abdomen revealed multiple areas of low attenuation in the liver and spleen consistent with multiple small abscesses. A diagnosis of typhoidal tularemia was suspected on the basis of the patient's exposure to documented tularemia in cats. An empiric therapeutic trial with tetracycline, 500 mg orally every six hours, led to a prompt defervescence and marked clinical improvement within 24 hours. The patient was discharged and completed an uneventful four-week course of oral tetracycline.

Serologic studies done at the time of his hospital admission showed normal Weil-Felix agglutinins, titers negative for brucellosis, psittacosis, and typhus, and a tularemia agglutinin titer positive at 1:320. At three months' follow-up, the patient did not have any relapse of his symptoms. Abdominal computed tomography showed resolution of the hepatic and splenic abnormalities. A tularemia titer during convalescence was positive at 1:640. Serologic studies obtained from his family members and veterinary associates were negative for tularemia.

Serology Survey

To determine whether the local veterinarians, who would have exposure to pets afflicted with tularemia, were at increased risk of contracting the disease, we obtained *F tularensis* agglutinin serologic tests (performed by the Northern Regional Laboratory, Fairbanks) of all 14 of the private veterinarians in the Fairbanks region. Elevated titers of 1:80 and 1:160 were present in two veterinarians (14%); brucellosis titers were negative. Neither seropositive person was involved in trapping or hunting.

Tularemia Survey

To assess whether the local medical community recognized the potential for tularemia in the Fairbanks area, we sent a questionnaire to the practicing local primary care physicians (internists, family practitioners, pediatricians, emergency department physicians; 28/33 responding) and veterinarians (12/14 responding). Of the 28 responding physicians, 15 (54%) were aware that tularemia was prevalent in the local wild mammal population and 11 (39%) were aware that local domestic animals were at risk of contracting tularemia and could transmit it to human contacts. Of the 12 responding veterinarians, 11 (92%) were aware that tularemia was prevalent in the local wild mammal population and that local domestic animals were at risk for contracting the disease; 9 (75%) had treated local domestic cats and dogs for tularemia in the past.

Discussion

This report demonstrates that typhoidal tularemia may result from cutaneous exposure to house pets, does occur far outside usually recognized endemic areas, and thus requires a high index of clinical suspicion for prompt diagnosis. Although generally considered to be an infection transmitted by wild mammals or arthropods in the south-central United States, tularemia may be encountered throughout Canada and the United States, except Hawaii. In 1991, 37 cases of tularemia were reported from the Pacific Northwest and Rocky Mountain states.[18] Knowledge of the diverse clinical presentations of tularemia and its routes of transmission is essential to the expedient diagnosis and proper management of an infected patient, as substantial morbidity and possible mortality may be avoided by prompt effective antibiotic treatment.[19]

Human tularemia can be categorized as two distinct clinical syndromes—ulceroglandular (including the glandular designation used in the older literature) and typhoidal, as observed in our first and second patients, respectively.[15] Isolated pharyngeal and pleuropulmonary presentations of tularemia are extremely rare. Pronounced local inflammation at the site of inoculation characterizes the ulceroglandular form, which carries a favorable clinical prognosis. In the typhoidal form of disease, limited local inflammation occurs, and morbidity and the risk of death are much greater.[15] Most cases of human tularemia occurring during summer are acquired from arthropod bites, whereas direct contact with infected mammals during hunting or trapping activities accounts for most human cases in the fall and winter months.[1-5,17]

Although reported to be present in only 26 of 62 patients (42%) reviewed recently,[15] the presence of a pulse-temperature dissociation, a characteristic of certain bacterial infections caused by intracellular pathogens, increased the clinical suspicion of tularemia in the cases reported here. Severe constitutional symptoms of high fever, chills, malaise, and headache were present in both of our patients. Lymphadenopathy and the complications of pneumonia, pericarditis, and pharyngitis previously reported in typhoidal tularemia were not observed. Gastrointestinal symptoms, including abdominal pain, anorexia, nausea, and diarrhea, were pronounced during the course of illness in both patients. Hepatic involvement was also present as demonstrated by the abnormalities on abdominal computed tomography—which resolved with appropriate antibiotic treatment—in patient 2 and elevated hepatic enzyme levels in patient 1. Elevated serum levels of at least one hepatic enzyme—lactate dehydrogenase, alanine and aspartate aminotransferases, and alkaline phosphatase—were reported in 58% of patients in a large series of tularemia.[15]

The laboratory diagnosis of tularemia is largely by serologic studies. Other laboratory tests for this disorder, including the leukocyte count and erythrocyte sedimentation rate, are extremely variable. Serum agglutinins are usually detectable by days 10 to 14 of infection; a fourfold rise in antibody titer is diagnostic. A single titer of 1:160 or higher in a patient suspected of having tularemia on clinical grounds is also considered diagnostic.[1-5,19] Titers may remain elevated for years after the acute episode. The formalin-fixed *F tularensis* used in agglutination reactions may cross-react with *Brucella* or *Proteus* O-19 antibodies, but the elevation in *F tularensis* titer is far greater than the titers to cross-reacting antigens.[1-5] Although immunity following tularemia is usually permanent, studies in animals suggest that cell-mediated immunity, rather than serum antibodies, confers protection.[20,21]

Before the introduction of antibiotics, the case-fatality ratio for tularemia was 5% to 15%. In recent years, reported mortality has declined to less than 1%, with typhoidal tularemia carrying the greatest risk.[1-5] Streptomycin is considered the drug of choice for tularemia, but gentamicin sulfate, chloramphenicol, and tetracycline are recognized as acceptable therapeutic alternatives.[1-5] An aminoglycoside should be used in the initial antibiotic regimen for the treatment of suspected tularemia in a patient with serious underlying disease.[19,22] In certain clinical situations, however, tetracycline is particularly attractive given its relative low toxicity and convenient administration compared with the other agents. When treating a seriously ill patient with tularemia, tetracycline may be used to complete a course of therapy following clinical stabilization with streptomycin or gentamicin. If used for this purpose, tetracycline therapy (2.0 grams per day orally) should be continued for three to four weeks to prevent relapses that may occur if therapy is limited to less than two weeks. Chloramphenicol can be substituted for tetracycline for the treatment of tularemia in children younger than 9 years. Response to appropriate antibiotic therapy is usually rapid, as seen in the two patients reported here, in whom notable clinical improvement was observed within 48 hours.[1-5,19] The importance of the early diagnosis and prompt initiation of appropriate antibiotic therapy against tularemia was emphasized in a recent report, where a delay in diagnosis and treatment correlated with a poor clinical outcome.[19]

In the Fairbanks, Alaska, region, the snowshoe hare (*Lepus americanus*), the local common native wild rabbit, is considered to be the predominant wild mammal host of *F tularensis;* hare ticks serve as the major pathogen reservoir.[23] Whereas about 1% of the American population is estimated to have an elevated titer for tularemia,[24] previous studies have documented that 3% to 7% of native Eskimos and Indians in central and western Alaska demonstrate serologic evidence of past exposure to *F tularensis.*[23,25] Although clinical tularemia is virtually nonexistent among native populations for unclear reasons, four cases of tularemia in white residents of the Fairbanks region were reported to the Alaska State Office of Epidemiology from 1982 to 1985. The two cases presented here represent the first reported instances of the transmission of tularemia by domestic animals in Alaska. Given the large reservoir of *F tularensis* in the snowshoe hare-tick population and the tendency of domestic dogs and cats to hunt and feed on sick prey, domestic pets in interior Alaska represent a potential vector for the transmission of *F tularensis* to human contacts. Furthermore, the finding that 14% of the veterinarians in the Fairbanks region had elevated tularemia titers (see Serology Survey) suggests that persons involved with domestic animal care should be regarded as a population at risk for tularemia in regions where *F tularensis* is enzootic.

Previous reports of cat-transmitted tularemia have described isolated cases of classic ulceroglandular tularemia.[7-9,11-13] The first case reported here is unique in that typhoidal tularemia developed following apparent exposure to an infected cat. Although veterinarians in the Fairbanks region were aware that local domestic animals were at risk for contracting tularemia, the potential for the transmission of tularemia from infected pets to human contacts was not generally recognized by the medical community (see Tularemia Survey), raising the possibility that additional cases of tularemia may have been misdiagnosed, possibly as unspecified viral syndromes.

Recognition of the possible vectors and diverse clinical presentations of tularemia can expedite the appropriate diagnostic studies and the initiation of appropriate empiric antibiotic therapy, thereby reducing potential morbidity and mortality. In regions where *F tularensis* is endemic in the wild mammal population, common domestic pets can acquire and transmit tularemia to human contacts. The finding that 48% to 62% of domestic dogs surveyed in two outbreaks of human tularemia had antibody titers to *F tularensis* of 1:40 or higher provides further evidence that common house pets may serve as hosts and vectors of the disease.[26,27] The high degree of virulence of *F tularensis* may allow for the transmission of tularemia to human contacts by bites or licks from apparently well domestic pets that harbor viable *F tularensis* organisms, acquired while preying on diseased wild mammals, in their mouths. Because *F tularensis* may survive in mud, water, or decaying carcasses for three to four months,[16] the carcasses of wild prey transported by pets to residential locations should be regarded as possible sources of *F tularensis*. Therefore, special care to avoid direct physical contact with mammal carcasses should be exercised in regions where tularemia is prevalent. Given the high virulence and substantial morbidity associated with *F tularensis*, physicians should consider the possibility of tularemia in a patient who presents with an acute febrile illness and a history of exposure to carnivorous domestic animals, including house cats, with access to the outdoors.

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Babesiosis in California

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BABESIOSIS IS A TICK-BORNE ZOONOSIS caused by an intraerythrocytic parasite. The cycle of transmission of the protozoan *Babesia* species between the tick vector and vertebrate host is occasionally interrupted by humans, resulting in human infection. Babesiosis is most common in otherwise healthy persons, many of whom remain asymptomatic. Although patients who have had a splenectomy are not more susceptible to infection with a *Babesia* species, they are more likely to become symptomatic, probably due to suppressed immune function. Symptomatic babesiosis is characterized by persistent fever and chills, hemolytic anemia, myalgias, fatigue, and hepatosplenomegaly. *Babesia divergens* causes severe and often fatal disease and is found throughout Europe. *Babesia microti*, found most often in the northeastern United States, typically causes a mild flulike illness, but a broad range of severity exists, and *B microti* babesiosis can be severe and occasionally fatal. Sporadic cases in other parts of America, often caused by non-*B microti* species, have been reported over the past 25 years, including two cases in California.[1,2] We report the third case of babesiosis contracted in California.

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Report of a Case

The patient, a 22-year-old male soldier, presented to Hays Army Community Hospital at Ford Ord, California, with fever and chills, headaches, nasal congestion, and vomiting of five days' duration. He had been on field exercises at Fort Hunter Liggett in central California when his symptoms first began. There he was prescribed penicillin V (previously called penicillin phenoxymethyl) at a battalion aid station when he reported a history of splenectomy in 1986 for idiopathic thrombocytopenic purpura. Symptoms persisted after several days of penicillin treatment, and when he began to complain of neck pain radiating down his back, he was admitted to the hospital. On admission he also noted generalized weakness, myalgias, and anorexia. He did not have sore throat, diarrhea, or productive cough.

He had spent most of the preceding year on field exercises in central California. He had not had recent mosquito or rodent bites but did recall a tick bite at Fort Ord, in the coastal region of central California, about five months previously without subsequent illness. He had no travel to the American Northeast, Wisconsin, or Minnesota within the previous year and had never traveled to Eastern or Western Europe, Africa, Asia, or South America. He had no pets and had not had close contact with any domestic animals including dogs, cattle, or horses. There was no history of blood transfusion or intravenous drug use. He had received a pneumococcal vaccine shortly before his splenectomy.

On physical examination the patient appeared lethargic but oriented. His temperature was 39.4°C (103°F), his blood pressure was 136/70 mm of mercury, and pulse 98 beats per minute. The skin was without rashes or bite marks. There was neck pain that radiated down his back on neck flexion. The physical examination was otherwise unrevealing.

The initial laboratory blood findings are summarized in Table 1. A urinalysis was remarkable for 2+ protein and 10 to 15 red blood cells per high-power field. A lumbar puncture yielded clear, colorless fluid; the Gram's stain showed no organisms or cells; latex agglutination tests for *Streptococcus pneumoniae, Neisseria meningitidis,* and *Haemophilus influenzae* were negative; and

TABLE 1.—*Laboratory Blood Findings in a 22-Year-Old Man With Febrile Illness*

Variable	Laboratory Value: SI Units	Laboratory Value: Traditional Units
Hemoglobin	132 grams/liter	13.2 grams/dl
Hematocrit	0.40	40%
Leukocyte count	5.6×10^9/liter	5,600/μl
Platelet count	46.0×10^9/liter	46,000/μl
Westergren sedimentation rate	2 mm/hr	same
Electrolytes		
Sodium	128 mmol/liter	same
Potassium	3.9 mmol/liter	same
Chloride	89 mmol/liter	same
Bicarbonate	31 mmol/liter	same
Glucose	6.1 mmol/liter	111 mg/dl
Creatinine	97.2 μmol/liter	1.1 mg/dl
Blood urea nitrogen	4.3 mmol/liter	12 mg/dl
Alkaline phosphatase	1.6 μkat/liter	99 IU/liter
Aminotransferase*		
Aspartate	2.7 μkat/liter	163 IU/liter
Alanine	1.3 μkat/liter	79 IU/liter
Lactate dehydrogenase	25.5 μkat/liter	1530 IU/liter
Total bilirubin	34.2 μmol/liter	2.0 mg/dl

SI = Système International

*Formerly glutamic-oxaloacetic transaminase (aspartate) and glutamic-pyruvic transaminase (alanine).

the protein concentration was 280 grams per liter (28 mg per dl), and glucose 4.07 mmol per liter (74 mg per dl). The cerebrospinal fluid cell count was 7.0×10^6 total cells per liter (7 per μl) with 5.0×10^6 erythrocytes per liter and 2.0×10^6 leukocytes per liter (2 per μl)—0.60 (60%) lymphocytes and 0.40 (40%) monocytes. A chest radiograph and sinus series were normal. Cultures of blood, urine, and cerebrospinal fluid were started, and the patient was treated empirically with intravenous benzylpenicillin pending results.

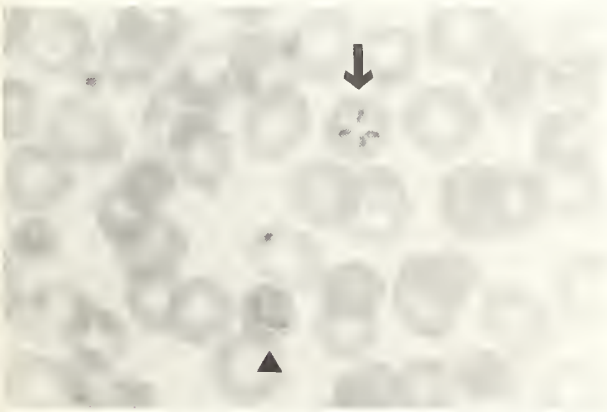

Figure 1.—A Giemsa-stained blood smear taken during the acute phase of the patient's illness shows a *Babesia* tetrad (arrow) and ring (arrowhead) (original magnification x 7,000).

On microscopic inspection of the blood smear (Figure 1), 1.2% of erythrocytes were found to be parasitized with small nonpigmented ring forms. Rare parasite tetrads were also observed, but no schizonts or gametocytes were seen. This established a preliminary diagnosis of babesiosis. Smears of serum and blood drawn within a week of presentation (acute phase) were sent to the Centers for Disease Control and Prevention (Atlanta, Georgia) for immunofluorescence testing and review. A titer of less than 1:8 for *B microti* returned, and parasite morphology was also consistent with non-*B microti* infection. Subsequent testing of the same serum specimen at the University of California at Davis veterinary laboratories revealed a positive titer of more than 1:64,000 to *Babesia gibsoni*. A Lyme assay was negative.

Treatment with quinine sulfate, 600 mg orally three times a day, and clindamycin phosphate, 1.2 grams intravenously twice a day, both for ten days, was instituted. The patient's symptoms began to subside within 24 hours. Parasitemia resolved after four days of treatment, as did hyponatremia, thrombocytopenia, hyperbilirubinemia, aminotransferase elevations, and proteinuria. Blood, urine, and cerebrospinal fluid cultures remained negative. He was discharged 11 days after admission without symptoms other than weakness, and five months later he reported no residual effects.

Discussion

Babesiosis is a tick-borne zoonosis of wild and domestic animals that causes substantial livestock loss worldwide.[3,4] It predates malaria as the first disease of vertebrates for which an arthropod vector was demonstrated.[5] Reservoirs include cattle, sheep, horses, cats, dogs, deer, and rodents. Babesia is transmitted by nymphal ticks of the *Ixodes* genus.[5] These ticks can also harbor *Borrelia burgdorferi*, and co-transmission of Lyme disease has been reported.[6]

Humans acquire infection accidentally and play no role in its transmission except in rare transfusion-associated cases[7-11] and one possible case of transplacental transmission to an infant.[12] The earliest human case was reported in Yugoslavia in 1957.[1] More than 200 human cases have since been reported worldwide in various age groups, including infants and children.[12-15] In the United States most infections occur between May and July on Nantucket and Martha's Vineyard islands (Massachusetts), Long and Shelter islands (New York), and the neighboring coastal areas; *Babesia microti* is the predominant infecting species, and the white-footed mouse (*Peromyscus leucopus*) is the primary reservoir.[16] Recently Connecticut has also emerged as an endemic area.[10,17,18] Sporadic cases have been reported in Washington State,[19] New Hampshire,[11] Wisconsin,[20,21] and Georgia.[20]

Only two cases of babesiosis have previously been contracted in California, one north of San Francisco (1966)[1] and one in central California (1979).[2] In both instances, immunofluorescence testing for *B microti* was negative. The previous rarity of infection in California can probably be attributed to the lack of an endemic *Babesia* species. The current report adds to a growing body of evidence that this situation may be changing. The case reported herein is the first in California for which a probable causative species, *B gibsoni*, is suggested.[1,2] To our knowledge, no other human case of *B gibsoni*

babesiosis has been detected in any region of the United States. *B gibsoni* is harbored in dogs and is endemic in Ceylon, Malaysia, Korea, and Egypt.[22] No canine infection with *B gibsoni* was reported in the United States until 1968, when it was detected in a dog imported from an endemic area in Asia.[23] Subsequently, only isolated reports from several states, each involving one dog, had been published in the veterinary literature until 1991, when Conrad and co-workers reported a cluster of 11 cases of *B gibsoni* canine babesiosis in Los Angeles, Kern, and San Bernardino counties.[22] None of these dogs had a history of out-of-state travel, suggesting that *B gibsoni* has become established in dogs in certain areas of southern California.

The geographic location, animal source, and vector of infection in this case all remain unclear. Although the patient had no pets and had had no exposure to domestic animals including dogs, it is certainly likely that there were many dogs living nearby and that any one could have traveled to or been imported from an area of California in which *B gibsoni* is found. Alternatively, *B gibsoni* may now be established in wild or domestic animals (or both) native to central California, with which the patient could have come in contact while at home or on field exercises. Finally, although *Ixodes pacificus* is the suspected vector for babesiosis in California,[19] confirmation of transmission by this tick is lacking. Seroprevalence studies of humans, wild and domestic animals, and ticks in California, similar to those previously done in the eastern United States, will be required to help answer these questions.

Pathophysiology

Babesia species multiply within erythrocytes, resulting in mechanical and probably autoimmune hemolysis.[24] Cellular immunity represents the primary line of defense. T lymphocytes activate macrophages, principally in the spleen, and induce the release of factors toxic to the parasites.[25] Thus, splenectomy worsens the course of infection. Infected patients have decreased numbers of T-suppressor cells and an increased T-cytotoxic cell fraction, allowing increased T-helper cell induction of antibody-producing B lymphocytes.[26] Antibodies play a disease-modifying role; passive transfer decreases parasitemia but does not prevent infection.[27] Advanced age and immunodeficiency also predispose to severe illness.[28,29]

Clinical Presentation

The typical incubation period of babesiosis is one to four weeks, although many patients never recall a tick bite. There is a gradual onset of fever, chills, myalgias, and fatigue. The "picket fence" temperature curve seen with malaria is conspicuously absent. A physical examination is typically unrevealing except for fever and in some cases mild hepatosplenomegaly. Laboratory investigations usually show a hemolytic anemia of mild to moderate degree; parasitemia tends to be less than 10%.[3] Leukocyte counts are often depressed, and thrombocytopenia is frequently observed.[10] Alkaline phosphatase, liver aminotransferase, and bilirubin levels are typically slightly increased, and electrolyte levels are usually normal. Although these findings characterize most cases of babesiosis, a broad range of severity exists, and infections complicated by the adult respiratory distress syndrome,[5,30] high-output cardiac failure,[20] severe neutropenia,[9] disseminated intravascular coagulation,[31] acute renal failure,[32] and retinal infarcts[33,34] have been reported.

The cause of the hyponatremia and proteinuria in this patient is not known. This is the first reported case of *B gibsoni* babesiosis in a human; thus, the clinical characteristics of infection with this species have not been previously delineated, and it is not known whether they differ notably from those described for *B microti* infections. These abnormalities, which resolved rapidly with treatment of the disease, may have been unique to the patient in question and not hallmarks of *B gibsoni* infection, but further human cases will be required to clarify this issue.

The diagnosis of babesiosis is made by examination of a Giemsa-stained thick blood smear (Figure 1).[35,36] *Babesia* parasites are pleomorphic, nonpigmented and ring-shaped, with an average diameter of 1.0 to 2.0 micrometers. Tetrads, representing dividing parasites, are rare but pathognomonic for *Babesia*. Schizonts and gametocytes are not seen. Diagnosis is often delayed due to the rarity of the disease and its superficial resemblance to malaria. Consultation with an experienced parasitologist may help differentiate among these pathogens and may aid in elucidating the infecting species of *Babesia* based on subtle but well-described morphologic differences apparent on blood smear (K. Ehnert, DVM, MPVM, Monterey County Epidemiologist, oral communication, November 1991).

Indirect immunofluorescence testing for antibodies to *B microti* is available from federal and state parasitology laboratories; a titer of 1:64 or higher constitutes a positive test at the California State Infectious Disease Laboratory; however, this criterion may differ at other laboratories. Immunofluorescence testing for antibodies to less common species is available at specialized veterinary and university research laboratories.

In healthy patients with a spleen, infection is often asymptomatic. Clinical illness, when present, may be fulminant or indolent; it may last weeks and include a convalescent period of as long as 18 months.[29] Whereas clinical illness eventually abates, parasitemia may not.[11] Relapses have occurred only in patients with the acquired immunodeficiency syndrome, who may require long-term suppressive therapy.[28] Only one reported case of American babesiosis—interestingly, in a patient with a spleen—has directly resulted in death.[30]

Treatment and Prevention

Patients with intact spleens may require only symptomatic treatment. Those without their spleen should be treated with antiparasitic drugs to decrease the severity of symptoms and ensure recovery. The regimen of choice is quinine, 650 mg orally three times a day, and clindamycin, 600 mg orally three times a day, or 1.2 grams given intravenously twice a day, for five to ten days.[3,8,20] Treatment failures have been reported,[11] and in these cases

exchange transfusion was curative.[9,11,37,38] Most of these patients were debilitated at the start or had a much higher degree of parasitemia than was seen in the case reported here.

Prevention is based on avoiding ticks.[4] When exposure is unavoidable, frequent body inspections should be done by individual and "buddy" systems. Nymphs should be detached immediately because the tick must feed for at least 12 hours before infection can be transmitted.[4,38] The use of diethyltoluamide-containing insect repellents is also recommended.[38] Unfortunately, transfusion-associated cases will probably continue to occur because widespread screening of donated blood products is not justified based on the low incidence of human infection. Babesiosis is a reportable disease in California (California Code of Regulations, sections 2502 and 2503).

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Rocky Mountain Spotted Fever Following Cardiac Transplantation

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ROCKY MOUNTAIN SPOTTED FEVER was first recognized in the early 1900s in the Snake River Valley of Idaho and the Bitterroot Valley of western Montana.[1] In 1909, Howard Taylor Ricketts established the ixodid tick as the vector for the disease.[2] Following the tick bite, the incubation period averages seven days (4 to 10 days), and the disease varies in severity and course. Typically a patient's temperature remains elevated to 39°C to 40°C (102°F to 104°F). A characteristic rash, a relatively late manifestation, may appear on the wrists and ankles and extend throughout the body, including the palms and soles. Initially there are erythematous macules that blanch with pressure, but after several days the rash becomes maculopapular and petechial. The rash begins to clear as the

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fever resolves, but lesions may remain visible for as long as several weeks. Widespread vascular damage may occur involving the skin, lungs, heart (myocarditis), brain, pancreas, liver, skeletal muscle, or kidneys. The endothelial cell injury leads to increased vascular permeability, edema, hypovolemia, and hypotension.[3]

The etiologic agent, *Rickettsia rickettsii*, is a pleomorphic coccobacillus that is an obligate intracellular parasite. It has ultrastructural similarity to gram-negative bacteria but is poorly visualized by Gram's stain.[4] The organism is more easily detected by direct immunofluorescence of tissue sections from areas of focal inflammation.[5] The primary target cell of rickettsial infection is the vascular endothelial cell. A focal lymphocytic vasculitis is seen on histologic sections of skin lesions. A few neutrophils may be present along with thrombosis and necrosis of the blood vessel. This cellular infiltrate is probably due to destruction of the endothelial cells by the rickettsial organism.[6]

Before the use of antibiotics, Rocky Mountain spotted fever carried a mortality of 15% to 20%.[7] With the use of tetracycline or chloramphenicol, mortality has been lowered to 3% to 6%, although the number of deaths among men, African Americans, and persons older than 40 years remains disproportionately high. Mortality is predictably increased by a delay in either diagnosis or initiation of treatment.[8] Fulminant disease—death within five days of onset—is seen in association with glucose-6-phospate dehydrogenase deficiency.[8] No reports of the spotted fever occurring in an immunosuppressed patient have appeared in the literature, however.

Report of a Case

The patient, a 27-year-old man, underwent orthotopic cardiac transplantation for a congenital mitral valve abnormality. His posttransplantation course was unremarkable, except for several episodes of mild rejection treated with increased immunosuppression. The patient was feeling well before riding for seven days on a cattle drive in southern Utah during the fall season. He traveled in brushy terrain but recalled no tick bites. Four days after his return, he reported myalgias, temperatures to 37.8°C (100°F), and chills. On the second day of the illness, his temperature rose to 40°C with sweats, frontal headache, and sore throat. On the fifth day of the illness, severe arthralgias of his knces, ankles, and metacarpophalangeal joints developed. A nonpruritic rash developed on his wrists and ankles and progressed to involve his palms, soles, and trunk. He did not have cough, earache, dysuria, nausea, or abdominal pain. He had not taken any new drugs except Co-Tylenol, a combination drug containing acetaminophen, chlorpheniramine, pseudoephedrine, and dextromethorphan. He reported several episodes of watery diarrhea without blood or mucus.

The patient was admitted to the University of Utah Medical Center on the fifth day of his illness, at which time his medications included cyclosporine, 180 mg twice a day; prednisone, 5 mg twice a day; captopril, 25 mg twice a day; aspirin, 80 mg a day; and azathioprine, 150 mg a day. He had no known allergies. On physical examination, his blood pressure was 142/70 mm of mercury, pulse rate 104 beats per minute, respirations 32 per minute, and temperature 39°C. The patient appeared cushingoid and diaphoretic with facial flushing, but he was in no acute distress. The cardiovascular examination revealed a prominent fourth sound and tachycardia. No obvious swelling or joint effusions were present in his extremities. Pain was induced by passive or active movement of numerous joints, being most severe in the ankles, knees, wrists, and metacarpophalangeal joints. The skin showed numerous erythematous, nonblanching, maculopapular lesions 2 to 5 mm in diameter scattered on the arms, legs, palms, and soles with a few lesions on his trunk. Several lesions on the lower extremity were petechial.

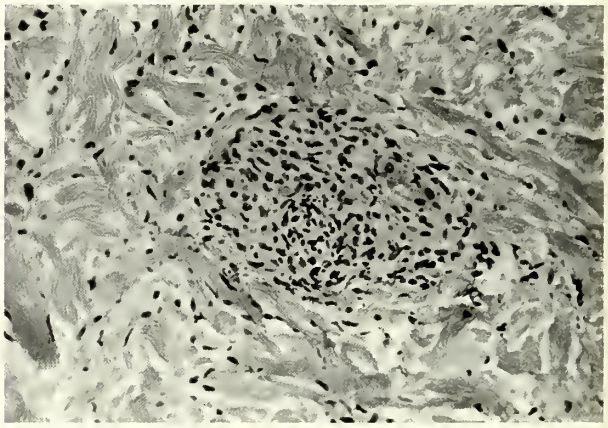

Figure 1.—Histologic examination of skin lesions shows a mononuclear cell infiltrate around the superficial dermal blood vessels (hematoxylin-eosin stain, original magnification × 620). This section was obtained on day 7 of the illness.

The laboratory evaluation revealed microscopic hematuria. Stool specimens were negative for occult blood and leukocytes. Serum electrolyte levels were within normal range. The total bilirubin concentration was 55 μmol per liter (3.2 mg per dl), direct bilirubin 10 μmol per liter (0.6 mg per dl), and the lactate dehydrogenase level was mildly elevated at 433 U per liter. The alanine and aspartate aminotransferase levels were normal. The hematocrit was 0.37 (a month previously it had been 0.41); the leukocyte count was 4.0×10^9 per liter (4,000 per μl) with 0.58 neutrophils, 0.20 band forms, 0.16 lymphocytes, and 0.06 monocytes. Serum analysis for antinuclear antibody was less than 1:40, and a Monospot slide test was negative for infectious mononucleosis. The prothrombin time was 17.4 seconds with an international normalized ratio of 1.2; the partial thromboplastin time was 40 seconds. Serum titers were negative for antistreptolysin-O, Epstein-Barr immunoglobulin (Ig) M, and cytomegalovirus IgM. Rubella and rubeola titers were negative. Biopsy specimens of palpable lesions obtained from the lower extremity on the seventh day of the illness revealed leukocytoclastic vasculitis (Figure 1); periodic acid-Schiff and Gram's stains were negative. A day later a second skin biopsy of a palpable lesion on the left upper extremity was

taken, and sections were stained by indirect immunofluorescence for IgG, IgM, IgA, and C3 with negative results.

On the tenth day of his illness, the patient continued to have chills, severe arthralgias, and a fever to 40°C. Cultures of multiple blood and urine specimens were negative. By that time, the rash was more clearly petechial and had progressed to involve more of his trunk, face, and right conjunctiva. Acute-phase serologic reactions with *R rickettsii* returned negative (less than 1:64). Because of his progressive skin lesions and persistent fever, it was decided to treat the patient empirically for Rocky Mountain spotted fever with doxycycline, 100 mg given intravenously every 12 hours. Within 8 to 12 hours he defervesced, and by hospital day 8 he felt well enough to be discharged on a regimen of oral doxycycline, 100 mg twice a day. At this time the skin lesions had cleared on his trunk, were slowly clearing on his upper extremities, but remained on his lower extremities. His arthralgias had completely resolved.

The current recommendation for antibiotic therapy for Rocky Mountain spotted fever is a seven- to ten-day course[9]; our patient was treated with a three-week course of doxycycline because of his immunosuppression. He did well without a recurrence of skin lesions or symptoms despite the continuation of immunosuppressive therapy. The serologic test at day 70 of the illness was again negative at less than 1:64.

In view of the presumptive diagnosis of Rocky Mountain spotted fever, further staining was done on the biopsy tissue obtained on the tenth day of the illness. This showed typical spotted fever-group rickettsiae using a fluorescein-conjugated polyclonal anti-*R rickettsii* antibody.[10] Further confirmation of the diagnosis was provided when a serum specimen obtained five months after infection had a titer of 1:640 when tested by the indirect fluorescent antibody (IFA) method using *R rickettsii* antigen. In an attempt to exclude possible infection by normally nonpathogenic spotted fever-group rickettsiae, which would be serologically cross-reactive by the direct immunofluorescence method, an indirect immunofluorescence method was adopted using an *R rickettsii*-specific murine monoclonal antibody against a 135-kilodalton species-specific major outer membrane protein of *R rickettsii*. A previously reported method was used that was further modified by the use of a fluorescein-conjugated antimouse immunoglobulin as a second stain.[5,11] The monoclonal antibody did not cross-react with *Rickettsia conorii, Rickettsia australis, Rickettsia akari, Rickettsia montana,* or *Rickettsia sibirica* (J.S.D., unpublished data), and its specificity has been confirmed by Western immunoblot.[12] By this method, *R rickettsii* organisms were visualized in the frozen sections of the skin biopsy, thus strengthening the identity of the specific etiologic agent in this patient.

Discussion

This patient displayed characteristic features of Rocky Mountain spotted fever infection. He presented with fevers and skin lesions typical of a rickettsial disease, and a skin biopsy revealed vasculitis. The presence of rickettsiae within a lesion was shown by immunofluorescent staining for spotted fever group-specific antigens. His response to doxycycline therapy was characteristic of an immunocompetent person with rickettsial infection.

This case is unusual in several respects. Our patient had no recollection of tick exposure; however, less than half of patients with this condition remember the tick bite. Rocky Mountain spotted fever is more frequently seen in the southern Atlantic states; Utah is not an endemic focus. In 1990, the Centers for Disease Control reported 649 cases of the disease, 16 of which were from the western United States and only 3 from Utah.[13] Between 1960 and 1990, there were only 16 cases reported to the State Health Department in Utah. In addition, the disease is more prevalent in the summer months, although this may correlate with tick exposure.

Another unusual aspect of this case is that the patient's serologic tests for Rocky Mountain spotted fever were negative at days 14 of illness and 70 of convalescence. The initial test was done at the University of Utah laboratory using a commercial kit (Hillcrest Biological, Cyprus, California) that detects IgG and IgM antibodies for *R rickettsii* by IFA. Characteristically, the initial IgM class antibody appears by day 8 of primary infection, with IgG detected about day 12. The IFA assay directed against both classes of antibody has been shown to be 95% to 100% sensitive seven to ten days after the illness begins.[14] Furthermore, serologic evidence of previous infection should be detectable beyond 100 days after the onset of the disease.[15] In our case, a serum specimen obtained 150 days after active infection revealed a titer of 1:640 by the IFA method using the rickettsial antigen. We speculate that the delay in mounting an antibody response in this patient was related to the patient's ongoing regimen of prednisone and azathioprine, which are known to dampen immunoglobulin production. In addition, cyclosporine is known to inhibit interleukin-2 production, which limits clonal proliferation of activated cycling B cells and thereby antibody production.[16] Thus, these factors may have contributed to our inability to detect an antibody response earlier in our patient's clinical course.

Recent studies have shown that cell-mediated immunity plays an active role in resistance to rickettsial organisms. Paradoxically, a transient immunosuppression may be seen with clearance of the organism.[17,18] A T-lymphocyte host response including interferon gamma production appears to be important in combating rickettsial infections.[19] Cyclosporine, azathioprine, and prednisone are all potent inhibitors of cell-mediated immunity. The patient presented in this case was taking high doses of cyclosporine and intermediate doses of azathioprine and prednisone. Despite these medications and the absence of detectable antibody during the acute phase, he never became seriously ill. He did have an atypically prolonged course but responded promptly and fully to treatment with appropriate antibiotics. This case suggests that T-cell–mediated mechanisms may be less important than previously thought. Another possible explanation for the unex-

pectedly benign course includes opportunistic infection with a spotted fever-group rickettsial organism that is usually nonpathogenic.

Many nonpathogenic rickettsiae such as *Rickettsia bellii, R montana, Rickettsia rhipicephali,* and *Rickettsia parkeri* have been isolated in the United States.[20,21] They may have antigenic similarities to *R rickettsii* that could produce a false-positive histochemical result in an immunofluorescent test based on the group-specific antigen. We attempted to exclude this possibility by using a murine monoclonal antibody developed against a species-specific major outer membrane protein of *R rickettsii* that is known not to cross-react with *R conorii, R australis, R akari, R montana,* or *R sibirica.* Staining by this technique was positive in our patient. Because this monoclonal antibody has been tested only against one of the nonpathogenic spotted fever-group rickettsiae known to occur in the United States (*R montana*), we are unable to exclude the possibility that the reagent might react with some of the other nonpathogenic tick organisms known to be present in Utah.

Perhaps the exogenous immunosuppression in our patient with a heart transplant provided protection from self-directed attack by the patient's immune system, thereby lessening the endothelial cell damage and resulting vasculitis. Recent investigations with animals suggest that this is not the case. Athymic mice, mice deficient in T cells and B cells, and guinea pigs treated with cyclophosphamide are not protected from immunopathologic responses associated with rickettsiae.[22]

In summary, we have presented a case in which a transplant patient acquired and fully recovered from Rocky Mountain spotted fever despite continuous treatment with potent immunosuppressive medications. Both humoral and cell-mediated immunity are thought necessary to combat rickettsial infections. Unexpectedly, our patient had a benign clinical course and an excellent response to antibiotics despite suppression of both his antibody and cell-mediated immune systems. This suggests that either the patient was infected by nonpathogenic rickettsial species or that other important mechanisms of defense against rickettsial infection exist.

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Commentary

Way of the Healer—The Work of Healing and the Healing of Work

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It is always a mistake to complain about the circumstances of our life, for they are the outward expression of what we are ourselves.

The Mother of Pondicherry
SRI AUROBINDO[1]

As a practice and profession, health care is being scrutinized as never before. Economic, political, and social pressures affect the institutions and individuals involved in health care in profound and far-reaching ways. From cost containment to access to rationing, our principles and practices as health care professionals are questioned, analyzed, and monitored. We are confronted with external pressures and influences that stimulate internal responses of anger, frustration, and resignation. Wisdom from other systems of medical practice and healing can help us adapt to the contemporary challenges of our personal and professional lives.

In western societies, relief from disease and the restoration of health and healing are often considered to come from professionals, trusted community representatives, hospitals, pharmaceutical agents, and technologic devices and maneuvers. Yet, we know from our own experience and the experiences of other cultures that diet, movement, touch, aroma, sound, quiet, solitude, light, beauty, plants, animals, and prayer also have healing effects. The knowledge implicit in this recognition, along with the realization that we are responsible for our own health, opens us to the truth present in healing practices and traditions other than those of contemporary western biotechnical medicine. An open-minded, multicultural exploration of other ways of knowing and healing does not require us to leave our tradition but, rather, to learn to listen to the truths of other traditions.

By such listening, we can better appreciate the contributions of traditional Chinese and Tibetan medicine, ayurvedic medicine, tribal healers, and many other practices. These systems, along with western medicine, are like fingers on the same hand, tributaries of the same river, wells tapping into the same aquifer. All are aspects and means to restoring health. Varied healing practices are all part of the "Great Medicine" of Native Americans, a concept that involves living in perfect harmony with the Earth and the "Great Mystery." Each tradition offers something to the big picture. There are many paths. Often the paths appear to merge, as can be seen in a thought recorded early in the 20th century by the Indian philosopher, Sri Aurobindo:

> We laugh at the savage for his faith in the medicine man; but how are the civilized less superstitious who have faith in the doctors? The savage finds that when a certain incantation is repeated, he often recovers from a certain disease; he believes. The civilized patient finds that when he doses himself according to a certain prescription, he often recovers from a certain disease; he believes.[1(pp65-66)]

In both traditions, belief is important despite the occurrence of different physiologic processes.

An expanded view of health and healing challenges how we perceive ourselves, our patients, our institutions, and our world. Albert Einstein said that "... the unleashed power of the atom has changed everything except our way of thinking. We need an essentially new way of thinking if mankind is to survive." We cannot continue to look at the body merely as a cholesterol level, a broken bone, a transplanted organ, or "the gallbladder in room 455." We can look at our body as a machine, or we can see it as a physical vehicle of our earthly journey. We can look at the body as a trap, or we can see it as a temple. We can look at the body as clay, or we can see it as the ether, the void, a great emptiness filled with potential—certainly a view not dispelled by particle theory or the "new" physics. In fact, the methods and truths of science and scientific inquiry in no way obstruct our capacity to accept truths from other sources. Science and scientific method provide us a fluid path with which to accept changes as knowledge expands. The flat world of Columbus's time gave way to new ideas; Newton's concept of physics has been supplanted by Einstein's. We need to expand our conception of our health care institutions as well. The hospital too often is described with negative connotations as prison, repair shop, or department store. Considering what goes on there—birth, healing, death—the hospital would better be seen as a temple, a sanctuary, a garden.

The seeking of health is a powerful and accessible metaphor. It is a metaphor for the search to comprehend the mystery that pervades our existence. In the pursuit of

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health, we are seeking to create balance, harmony, and joy, to eliminate pain and suffering, and to gain knowledge, understanding, and truth. This is a dynamic, evolutionary, personal quest into the mystery that surrounds us—our professional struggle with illness recapitulates our personal struggle with meaning. Here, the scientific and spiritual searches for truth overlap. Technology and mythology meeting at the boundary of seen and unseen, measurable and unmeasurable, matter and energy. By adding the vision and wisdom of other traditions to our own, we become better equipped for this metaphoric exploration.

How do we go about this expansive, multicultural search, this personal journey, and this professional work? How do we honestly and healthfully respond to the challenges and demands of our lives? Is there a way of the contemporary healer? Two suggestions from Aurobindo can guide us:

- If you want to change the world, first change yourself; and
- It is only in quietness and peace that one can know what is the best thing to do.

To be effective, compassionate, and generous healers, we must first heal ourselves. We must have the courage, will, and determination to be generous and compassionate with ourselves. In part, we do this by acknowledging the need for quiet, for calm, for stillness to pursue our personal search for truth. This might take the form of mindful work, relaxation, study, walking, jogging, prayer, meditation, or any number of other techniques. It does require, regardless of the form, that we change, avoid, and ignore or forgive the relentless din of often mindless distraction and meaningless noise that engulfs us much of the time. Only in a state of quiet calm can we begin to hear the voice of our inner truths.

As we encounter and deal with the challenges of medical practice, we must acknowledge that these circumstances reflect, not define, our lives. Our work needs fill us, not empty us. If creating health and healing are our work, they should be practiced in the spirit of Gibran's prophet:

> Work is love made visible. . . .
> For if you bake bread with indifference,
> You bake a bitter bread that feeds but half man's hunger.
> And if you grudge the crushing of the grapes,
> your grudge distills a poison in the wine.
> And what is it to work with love?
> It is to weave the cloth with threads drawn
> from your heart, even as if your
> beloved were to wear that cloth. . . .
> It is to sow seeds with tenderness and
> reap the harvest with joy even as if
> your beloved were to eat the fruit.
> It is to charge all things you fashion
> with a breath of your own spirit.[2(pp27-28)]

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Editorials

On 'Downsizing' Health Care

As this is written, two giants of American economic growth and industrial achievement are undergoing unprecedented "downsizing," that is, they are substantially reducing the size of their organizations and the scope of their industrial operations. General Motors Corporation (GM) and International Business Machines, Inc (IBM) were considered among the best in the industrial world. They set standards for American enterprise and technologic success. Both prospered, but as they did, their corporate infrastructure grew and with it, the number of employees and the costs of administering and operating such large, complex organizations. The needs and interests of the corporate infrastructure began to displace the perceived needs and interests of the public that was to consume their products. General Motors began to build large cars when the public wanted small ones, and IBM placed its bets on large mainframe computers while the public was turning to smaller computers that could be linked to one another more or less as needed. Both began to lose money, and the costs, which were rising, finally became unacceptable. The corporate solution mandated by the rising and uncontrollable costs was to downsize what had been paragons of American economic growth and achievement. This was done by closing unprofitable plants, eliminating a great many jobs, and trying to be more responsive to consumer needs and expectations.

There would seem to be some parallels in health care. American health care is generally considered to be the best in the world. It is certainly the most technologically advanced. It has surely prospered. The infrastructure and the number of jobs within the health care system have grown enormously. The costs continue to rise and are now considered by many to be unacceptable. The system's interests are not always responsive to what the public or health care consumers need or expect. Nearly 30 million Americans have no health insurance with which to access the system. Yet America spends more dollars per capita on health care than any other developed nation. Other industrialized nations seem to be doing better. One can make an argument for a parallel need to downsize the American health care system and for some better responsiveness to consumer needs.

Corporations are at an advantage for accomplishing effective downsizing within their organizations. There is relatively centralized control. The corporate executives and the boards of directors represent the stockholders who in fact own the company. They are in a position to restructure the system from within by fiat. They can be ruthless and fire employees and close unprofitable plants more or less at will to accomplish the needed downsizing. And perhaps equally important, they need to serve only those consumers who are willing and able to pay for their products or services.

The health care system, on the other hand, is at a comparative disadvantage when it comes to downsizing. Power in the system is spread widely and is therefore diffuse. It is unlikely, if it has not already been demonstrated, that in this nation any single authority will ever be able to govern health care. The ownership is widely distributed throughout both the public and private sectors. It is now the largest industrial enterprise in the nation. There are many jobs, professions, and other entrenched political forces to be taken into account. And, further, the system must somehow serve those who cannot pay for needed products or services that the system provides. Yet, some form of downsizing seems as necessary for a high-cost health care system as it has proved to be for GM and IBM and for many of the same reasons.

There are similarities between what must be done in GM and IBM and what must be done in health care. Both need to pay more attention to consumer needs and expectations. Both need to improve efficiency and reduce the cost per consumer served. Both need to promote and accommodate progress and change. Both need to increase the size of their market and serve more consumers.

In health care there may already be more than enough dollars, since we are already spending more per capita than any other nation. There are many underserved consumers who receive inadequate or inefficient care—or none at all. Downsizing in health care might better be viewed as downsizing the enormous and ever-increasing overhead waste and inefficiency that now pervade the system and somehow reallocating the dollars thus saved to meet the basic needs of all consumers and, of course, including those who are presently without adequate access. Done well, this could stabilize the rise in health care costs, increase the size of the consumer market for health care, and avoid too great an overall job loss in the health care system. Downsizing in health care would then eliminate much of today's costly excess baggage, but this would be eased by a countervailing extension of products and services to a presently underserved market. However, the temptation to do this by fiat should be resisted because, unlike GM and IBM, the health care system is multifocal with a wide range of ownerships and power bases, and all must act in concert if there is to be efficiency and ultimate success. Collaboration rather than coercion would seem more likely to achieve a desired result. Even so, there may be lessons to be learned from the downsizing experiences of GM and IBM.

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Hansen's Disease—A Time for Cautious Optimism

Hansen's disease, or leprosy, is an ancient human malady. The causative organism, *Mycobacterium leprae*, is an exquisitely adapted human pathogen, capable of multiplying to incredible numbers in susceptible hosts while

rarely killing its victims. Similarly, the innate resistance present in 80% to 90% of the population is consistent with long-term selective pressure on the genetics of the human immune system. Whereas complete control or eradication of leprosy is not a realistic goal for the foreseeable future (despite the wishful thinking of the World Health Organization[1]), the world situation with respect to leprosy is more hopeful than at any time in the past 20 years.

The historical epidemiology of leprosy in the United States and western Europe is complex and controversial, but there is universal agreement that the prevalence of leprosy rapidly declined in the late 1800s and that the disease had virtually disappeared from many countries (including Norway, the home of Armauer Hansen) by the 1920s. The explanation for this phenomenon, which took place decades before the discovery of effective chemotherapy, is unknown. This is in stark contrast to the situation in many developing countries of Africa, South America, Southeast Asia, and the Indian subcontinent. Leprosy continued virtually unchecked in these regions, despite control programs initially based on the principle of isolation and subsequently on single-drug therapy with dapsone. In 1966 it was estimated that there were approximately 11 million cases of leprosy in the world. Estimates over the next two decades were consistently in the range of 10 to 12 million cases. This may not be as dismal as it first appears, since the population at risk more than doubled over this 20-year period, but it was discouraging to leprosy workers who had hoped for more dramatic evidence of the efficacy of their control programs.

This evidence may now be in hand. Global epidemiologic data are notoriously suspect, particularly when the disease in question primarily affects the rural poor in developing countries. Nonetheless, there is a growing body of evidence suggesting that dramatic changes have recently taken place in the epidemiology of Hansen's disease. New data from the World Health Organization estimate that the number of active cases of leprosy in the world in 1991 had decreased to 5.5 million.[2] Noordeen and co-workers speculate that this dramatic change likely reflects many concurrent developments: the implementation of multidrug therapy in the early 1980s with its shorter treatment durations and precise definitions of cure, increased leprosy surveillance efforts as part of the multidrug-treatment program, possible residual effects from preexisting dapsone monotherapy programs, and naturally declining trends in some areas. Fine thinks that intensive vaccination programs with bacillus Calmette-Guérin (BCG) may have also contributed to this striking decrease.[1]

There is more good news in the area of chemotherapy for leprosy. The move to multidrug-treatment regimens in the early 1980s was primarily a response to the concern over the rapidly increasing problem with dapsone resistance. So-called secondary dapsone resistance developing in multibacillary patients after years of dapsone monotherapy and manifesting as recrudescence of active clinical disease had been recognized for many years. It was not until the late 1970s, however, that dapsone resistance in newly diagnosed patients (primary dapsone resistance) became a substantial problem. There was also growing concern about the possible emergence of rifampin and clofazimine resistance. It rapidly became apparent that the additional difficulty and expense of treating patients with resistant disease offset the disadvantages of multidrug therapy—increased drug costs, supervised administration, and toxicity. By the mid-1980s most countries had adopted some variant of multidrug therapy.

It is fair to say that the results have exceeded expectations. The prevalence of high-level dapsone resistance, particularly primary resistance, has not increased and may be on the decline. Resistance to other antimycobacterial agents remains extremely uncommon. Many patients who had been maintained on clinic rosters for years were declared cured and were discharged. This in turn freed up personnel and funds for associated activities such as case finding and rehabilitative care for patients with residual deformities (estimated to number 2 to 3 million worldwide).[2]

Stable or diminishing drug resistance and the apparent effectiveness of a shorter duration of chemotherapy is not the end of the good news. In contrast to the dismal situation with *Mycobacterium tuberculosis* and *Mycobacterium avium*, in recent years several new agents with excellent activity against *M leprae* have been developed and tested, including minocycline, ofloxacin, and clarithromycin. Several other agents including fusidic acid, brodimoprim, various clofazimine derivatives, and the combination of imipenem and cilastatin sodium have also shown some promise. Given their high cost relative to the currently used drugs, it is unclear exactly what role these new agents will play in the routine management of Hansen's disease. While there is some hope that enhanced bactericidal activity will make shorter treatment courses possible, the slow multiplication rate and low metabolic activity of *M leprae* may be limiting factors. Antibiotics, in common with essentially all chemotherapeutic agents, exhibit maximal activity against actively replicating and metabolically active cells. The lethargic nature of *M leprae* may place practical limits on the minimum duration of chemotherapeutic regimens. Still, for the foreseeable future, and certainly for the remainder of this decade, the world possesses an adequate therapeutic armamentarium to treat Hansen's disease.

In the past decade there have also been dramatic advances in our understanding of disease pathogenesis and host immunity in leprosy. The cellular constituents of leprosy lesions have been characterized for the different classes of disease, and the web of cytokine interactions is slowly being untangled.[3] A good example of the clinical importance of this work is seen in our new understanding of erythema nodosum leprosum, a common and sometimes life-threatening complication of multibacillary leprosy. Erythema nodosum leprosum was long thought to be an immune complex disease, based on clinical and histopathologic similarities to experimental and naturally occurring immune complex diseases. This hypothesis, however, failed to explain the therapeutic efficacy of

thalidomide, which has no activity in classical immune complex disorders, or the fact that immune complexes could not be consistently detected in patients with erythema nodosum leprosum. In 1987, we reported that cyclosporine, a specific inhibitor of interleukin-2 activity, was effective in controlling recalcitrant cases of erythema nodosum leprosum.[4] More recently it has been shown that levels of tumor necrosis factor-α (TNFα) are elevated in patients with this reaction and that thalidomide acts by selectively inhibiting TNFα.[5] If this finding is confirmed, there is a strong possibility that one or more of the anti-TNF agents currently under development will provide a therapeutic alternative for erythema nodosum leprosum without the toxicity of thalidomide or cyclosporine.

Despite these dramatic developments, there remain several areas of concern or where further research is needed. It is critical that existing control programs in endemic areas be sustained or enhanced. It is also essential that clinicians remain vigilant for the emergence of drug resistance and that research into new drug development continue. The recent experience with tuberculosis should be a lesson in the hazards of complacency and the necessity to maintain a strong control program even when a disease is waning in prevalence.

There is a need for epidemiologic studies to document the extent of the decrease in the prevalence of leprosy and to gather accurate information on the incidence of leprosy. These studies might also help to resolve the uncertainty concerning the mode of transmission of *M leprae*.[6] A rapid decline in disease incidence during an active multidrug therapy-based control program would be consistent with a primary role for human-to-human transmission, whereas a stable or slowly declining incidence might suggest acquisition of *M leprae* infection from the environment. Taken to its logical conclusion, if epidemiologic studies indicate that *M leprae* is simply one of the numerous species of environmental mycobacteria, then simple measures such as providing clean water or shoes for children might be the most cost-effective control strategy.

Progress towards the goal of eradication will also depend on continued support for basic research. There is a desperate need for a diagnostic test that can be done under field conditions by personnel without advanced laboratory or pathology training. As summarized by Gelber, existing serologic tests lack sufficient predictive value for active disease.[6] Preliminary results with assays using the polymerase chain reaction are more promising, but much remains to be done. Improved methods for antimicrobial sensitivity testing would greatly accelerate the process of screening novel compounds for activity against *M leprae* and for detecting drug resistance. Finally, there remains the hope that the growing understanding of the immunology of leprosy will facilitate the design of a vaccine that will consistently produce protective immunity.[7]

These are exciting and optimistic times in the field of leprosy. The work of innumerable researchers and health care professionals is finally beginning to bear fruit, and there is the real possibility of continued dramatic declines in the number of cases. At the same time, it must be remembered that the worldwide epidemic of human immunodeficiency virus infection is placing unprecedented demands on the limited health care budgets of many of the countries where leprosy is highly endemic. The next decade promises to be as exciting and eventful as the one that has just drawn to a close.

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The Enigma of Graves' Ophthalmopathy

AN EXPLANATION FOR THE ASSOCIATION of hyperthyroidism with eye disease has long been sought. In 1835, Robert Graves described the case of a 20-year-old woman with weakness on exertion, weight loss, and tachycardia[1(p36)]:

> [T]he eyes assumed a singular appearance, for the eyeballs were apparently enlarged, so that when she slept or tried to shut her eyes, the lids were incapable of closing. When the eyes were open, the white sclerfae] could be seen to a breadth of several lines, all around the cornea. In a few months, the action of the heart continuing with unceasing violence, a tumor of a horseshoe-shape appeared in the front of the throat and exactly in the situation of the thyroid gland.

Although advances have been made in our understanding of Graves' ophthalmopathy since this early description, we still lack the insight needed to design all but essentially palliative therapy for our patients with this disorder.

Investigations concerning the pathogenesis of Graves' ophthalmopathy have been difficult to undertake, largely because there is no animal model for this condition and because of the relative scarcity of affected human orbital tissues available for study. Because the hyperthyroidism of Graves' disease is caused by circulating antibodies directed against a thyroid antigen (the thyroid-stimulating hormone [TSH] receptor), early studies of ophthalmopathy were aimed at detecting autoantibodies directed against orbital antigens. These studies were complicated by the use of porcine tissues by investigators lacking access to human tissues and by the use of crude human tissue preparations that did not allow an exact definition of the cells being studied. Indeed, even today there remains controversy concerning precisely which orbital cell is the target of autoimmune attack in the disease. In addition, it

is unclear whether circulating antibodies reported to be directed against orbital fibroblasts and muscle cells are primarily pathogenic or whether they arise secondarily as a result of the inflammatory process in the orbit.

From a mechanical standpoint, the signs and symptoms of Graves' ophthalmopathy are understood to result from an increase in volume of the soft tissues (connective and muscular) contained within the confines of the bony orbit. The resultant orbital increase in pressure produces forward displacement of the globe and obstruction of venous drainage. These anatomic changes lead to proptosis, periorbital edema, lid edema, chemosis, and conjunctival congestion. Optic neuropathy may be on an ischemic or compressive basis. Early in the disease, the extraocular muscles function poorly due to swelling of the muscle bodies. In late stages of the disease, fibrosis with restriction of these muscles becomes apparent and accounts for their dysfunction.

Many studies have examined the myocyte as a possible target cell in Graves' ophthalmopathy, owing to the massive enlargement of extraocular muscle bodies apparent in tissue specimens and by computed tomographic scanning. Histologic examination of the tissues of the orbit reveals the muscle cells themselves to be intact, however.[2] This has been shown by light and electron microscopy and by electromyography. An accumulation of glycosaminoglycans (GAGs), hydrophilic mucopolysaccharides, is apparent both within the orbital fatty connective tissues in the posterior orbit and within the endomysial connective tissues surrounding the extraocular muscle cells. This accumulation of GAGs, with its attendant edema, results in gross enlargement of the extraocular muscle bodies and swelling of the surrounding orbital connective tissues. Further, histologic examination of pretibial skin biopsy specimens from patients with pretibial dermopathy reveals a similar accumulation of GAGs within the dermal connective tissues.[3] Because GAGs are fibroblast products, the possible role of orbital and pretibial fibroblasts as autoimmune target cells in Graves' disease is of interest. Recent studies have examined the regulation of GAG production by these cells and their potential to express immunomodulatory proteins, such as HLA-DR, intercellular adhesion molecules, and a 72-kilodalton heat-shock protein.[4]

The close clinical association between Graves' hyperthyroidism, ophthalmopathy, and pretibial dermopathy suggests that there may be a common antigen in the thyroid, orbit, and pretibial skin that is recognized by circulating lymphocytes in Graves' disease. Certainly the TSH receptor itself would be a candidate, and recent evidence suggests that fibroblasts might have the ability to express this antigen. The existence, however, of euthyroid Graves' ophthalmopathy, of Graves' hyperthyoidism without clinically detectable ophthalmopathy or pretibial dermopathy, and of apparently unilateral ophthalmopathy is perplexing and must be explained. Several factors are likely involved in the development of the clinical disease, such as variances in orbital anatomy and the presence of many antigenic epitopes. It may be that there is general autoimmune involvement of connective tissue throughout the body in Graves' disease and that regional differences between fibroblasts (such as their abilities to produce particular matrix proteins or to express relevant immunomodulatory proteins) are responsible for the clinical expressions of the disease in the orbit and pretibial skin.

The clinical disease itself has been difficult to study, owing in great part to its diversity of presentation, spectrum of severity, and varied time course of expression. Some patients have severe proptosis with little periorbital edema, whereas others have massive periorbital edema with little proptosis. Still other patients may be bothered primarily by extraocular muscle dysfunction. Further, although clinically notable ophthalmopathy is apparent in only 20% to 40% of patients with Graves' disease, the vast majority of patients can be found to have at least subtle ocular involvement if sensitive imaging techniques are employed. Similarly, although only a few patients with severe ophthalmopathy have pretibial myxedema, histologic examination of the skin of patients with Graves' hyperthyroidism reveals subtle dermatopathic changes in the majority. Thus, Graves' ophthalmopathy and pretibial dermopathy may be considered nearly constant features of Graves' disease, with vastly varied clinical expressions.

Primarily because of the many facets of the clinical expression of Graves' ophthalmopathy, the "no specs" classification of Graves' eye disease was proposed in 1969 and modified in 1977 (Ad Hoc Committee of the American Thyroid Association, Werners Classification). Although this classification system functions well as a teaching device to illustrate the various signs and symptoms of the disease, its use in studies aimed at comparing the results of treatment has tended to obscure the often independent courses of the various components of the disease. Further, the numbered classification suggests that there is a continuous or stepladder progression of the disease, an assumption that does not coincide with clinical observation. The use of the "no specs" classification system to observe a particular patient with the condition is also unsatisfactory for the same reasons. Because of the limitations of this classification system, the International Thyroid Associations have recently urged that this system no longer be used for reporting the results of clinical studies. It is recommended instead that investigators specify the possible benefits of therapy and provide objective data—proptosis measurements, quantitation of extraocular muscle volume and function, measurements of visual acuity, visual fields, color vision—in support of each claim.[5]

In this issue of the journal, William Barrie, MD, presents a comprehensive overview of the diagnosis and management of Graves' ophthalmopathy.[6] He provides a careful and useful discussion of the available treatment options, including the precise symptom or sign of the disease for which each might be indicated. His approach also serves to delineate clinical circumstances in which a patient might best be managed in conjunction with an ophthalmologist, radiotherapist, endocrinologist, or a team of

specialists. Most important, as Barrie points out, each patient requires an individualized approach to management, aiming therapy at those components of the disease that are most troublesome to that particular patient.

There is currently no effective means to prevent ophthalmopathy or to predict which patients with Graves' hyperthyroidism are most likely to go on to have substantial eye disease. Further, because of possible medical side effects and risks inherent in the surgical procedures available, treatment is reserved primarily for patients with advanced, severe disease. While each of these options is useful in particular clinical situations, none specifically addresses basic pathophysiology; corticosteroids, other immunosuppressive agents, and radiotherapy likely function as general immune suppressants, in part by inhibiting the production of cytokines and other inflammatory mediators by activated mononuclear cells. Likewise, transantral surgical decompression of the orbit mechanically relieves the increased pressure within the orbit by allowing the soft tissues to decompress into the maxillary sinus, but does not directly affect the autoimmune process.

The introduction of specific therapeutic and preventive strategies awaits a more complete understanding of the pathogenesis of Graves' ophthalmopathy. For example, therapies directed at neutralizing the stimulators of orbital fibroblast GAG production or modalities that inhibit the expression of immunomodulatory proteins by orbital fibroblasts might be useful. Therapies aimed at earlier steps in the disease process await a delineation of the relevant orbital antigens and of the T-cell epitopes involved. The understanding of basic mechanisms responsible for the association of eye disease, skin disease, and hyperthyroidism will solve a long-perplexing puzzle. More important, it will allow the development of preventive strategies or more effective therapies for our patients with this painful, disfiguring, and sight-threatening disease.

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Is Frequent Marijuana Smoking Harmful to Health?

OVER THE PAST quarter of a century, marijuana has remained the most commonly abused illicit drug in our society. According to the most recent national survey, more than 25% of high school seniors and young adults 19 to 30 years of age in the United States report having used marijuana within the past year, about 15% within the preceding month, and 2.2% to 2.5% (3.2% to 5.3% of young men) daily.[1] These figures probably underestimate the actual prevalence of marijuana smoking, since national surveys underrepresent high-school dropouts and young adults who are difficult to contact by mail, among whom drug use is likely to be greater than among those surveyed. Because smoking is the preferred route of the administration of marijuana and the smoke of marijuana contains a number of respiratory tract irritants and carcinogens,[2] there is justifiable concern that, as with tobacco, the habitual smoking of marijuana over years to decades can produce clinically substantial lung damage and respiratory tract malignancy.

This concern is supported by several experimental studies in animals[3-6] and in vitro[7-9] that have found considerable toxic, inflammatory, and even carcinogenic effects of exposure to marijuana smoke on lung tissue and cells. Until recently, however, few studies have examined the long-term pulmonary effects of real-life heavy, habitual marijuana smoking in humans. Early clinical studies of the respiratory consequences of habitual marijuana smoking published in the mid-1970s yielded conflicting results,[10-13] possibly because of small sample sizes and the failure to control adequately for confounding factors such as concomitant tobacco smoking. A more recent comparison study of 144 heavy, habitual smokers of marijuana only, 135 smokers of marijuana plus tobacco, 70 smokers of tobacco only, and 97 control nonsmokers revealed an association between heavy regular use of marijuana (3 to 4 joints per day for >5 years) and symptoms of acute and chronic bronchitis,[14] dysplastic and inflammatory changes in tracheobronchial mucosa,[15] increased numbers of alveolar macrophages and neutrophils in bronchoalveolar lavage fluid,[16] and impaired microbicidal activity of alveolar macrophages from marijuana smokers compared with tobacco smokers.[17,18] These findings indicate that frequent marijuana smoking can cause airway injury, lung inflammation, and impaired pulmonary defenses against infection. Results of other recent studies, moreover, have documented depressant effects of marijuana components on macrophage and human neutrophil function,[19,20] human natural killer cell activity,[21] and human mononuclear cell cytokine secretion,[22] suggesting that marijuana use increases the susceptibility to infection.

Several lines of evidence suggest that marijuana smoking is also associated with an increased risk for the development of respiratory tract malignancy:

- The insoluble particulate (tar) phase of the smoke from marijuana contains about 50% more of some carcinogenic aryl hydrocarbons, including benz[*a*]anthracene (a weak carcinogen) and benzo[*a*]pyrene (a strong carcinogen), than the smoke from a comparable quantity of unfiltered Kentucky reference tobacco.[2]
- The painting of smoke condensate (tar) from mari-

juana cigarettes on the skin of mice led to the development of metaplastic and neoplastic lesions that correlate with carcinogenicity.[2,23]

• Hamster lung explants exposed to marijuana or tobacco smoke over a period of two years led to atypical proliferation and disturbances in cell structural features and genetic equilibrium that were more impressive after marijuana than after tobacco exposure. These changes were followed by an accelerated malignant transformation within three to six months of marijuana exposure compared with that found in control explants.[8]

• In the Ames Salmonella-microsome test, marijuana smoke condensate induced a number of mutations comparable to those produced by an equivalent amount of tobacco tar.[24]

• Extensive metaplastic and dysplastic changes have been noted in the bronchial epithelium of heavy, habitual marijuana smokers who underwent biopsies at randomly selected sites of bronchial mucosa by fiberoptic bronchoscopy.[15] Squamous metaplasia and dysplasia are considered to be precursors of bronchogenic carcinoma.[25]

• Several cases have been reported of respiratory tract malignancy—tongue, tonsil, pyriform sinus, paranasal sinus, larynx, lung—in relatively young, long-term, habitual marijuana smokers.[26-30] Taylor identified 10 patients younger than 40 years out of 887 patients of all ages in whom respiratory tract cancer had developed: 2 of the lung—squamous cell carcinoma and small-cell anaplastic cancer—4 of the larynx, and 4 of the tongue. Interestingly, of these ten patients, five were heavy users of marijuana, two were regular marijuana smokers, one probably used marijuana, and the remaining two had no known history of use, implicating marijuana as an important cause of respiratory tract cancer, especially in persons younger than 40.

• The smoking of one marijuana cigarette—800 to 900 mg, 1% to 3% Δ^9-tetrahydrocannabinol—led to the deposition in the lower respiratory tract of about a fourfold greater quantity of insoluble smoke particulates (tar) than did smoking a filtered tobacco cigarette of comparable weight,[31] thus amplifying the exposure of the marijuana smoker to the carcinogens in the tar phase and increasing the risk of respiratory tract carcinogenesis.

Despite the evidence, which supports the view that habitual smoking of marijuana causes lung damage and predisposes to respiratory tract infection and malignancy, some advocates of the legalization of marijuana argue that marijuana is a far safer substance than tobacco. Advocates of marijuana "reform" contend that tobacco is responsible for hundreds of thousands of deaths each year due to cardiovascular disease and respiratory illness, whereas no definitive evidence exists linking marijuana, which is usually smoked in far smaller daily quantities than tobacco, to serious morbidity or mortality. The paucity of information concerning the health consequences of frequent marijuana smoking has been attributed, in part, to the relative recency of the upsurge in marijuana use prevalence and the lengthy lag period between possible long-term effects, such as respiratory tract malignancy and chronic obstructive pulmonary disease, and the initiation of use. Therefore, sufficient time may not have elapsed for these long-term health effects to become clinically obvious, particularly in view of the relatively small percentage of habitual daily smokers of marijuana who would appear to be at higher risk than the casual user. A long lag period should not be required for the expression of other harmful effects of marijuana, such as acute respiratory illness—bronchitis, pneumonia—although an epidemiologic assessment of the risk of marijuana smokers for respiratory tract infection developing is complicated by the potentially confounding influence of the concomitant use of other substances, including alcohol and tobacco. One might conclude from the dearth of information concerning marijuana-related morbidity either that such health effects are too infrequent to be measured or that such effects are occurring at greater than expected frequency but have not been documented because of the lack of a systematic effort to "capture" these events.

A crucially important obstacle to efforts to study the health effects of marijuana smoking in the "real" world is the nearly universal failure of physicians to query their patients concerning the use of marijuana. As pointed out by Polen and colleagues elsewhere in this issue of the journal, physicians recorded marijuana use in the medical records of only 3% of marijuana smokers who reported daily or near-daily smoking of marijuana in a comprehensive health survey.[32] These authors are the first to use a systematic review of medical records to assess the health consequences of marijuana, controlling for the effects of tobacco, alcohol, and sociodemographic variables. Their finding that near-daily marijuana smoking is a significant independent risk factor for the development of respiratory illness, injuries, and other medical problems requiring medical attention challenges the view that marijuana use poses insignificant health hazards. The authors appropriately acknowledge that their data are preliminary and that further study is required to evaluate the effects of marijuana smoking over a longer follow-up period and to examine dose-response relationships and interactions with tobacco and other substances of abuse.

Polen and co-workers have usefully pioneered the use of medical records as an epidemiologic tool for expanding our limited knowledge concerning the health consequences of the second most widely smoked substance in our society. The feasibility of this investigative strategy, however, depends on the diligence and consistency of physicians in incorporating into their routine history taking nonjudgmental questions concerning whether and to what extent their patients are using or have used marijuana, as well as other illicit drugs, and including this information in the medical record. Although more information is certainly needed, sufficient data have already been accumulated concerning the health effects of marijuana to warrant counseling by physicians against the smoking of marijuana as an important hazard to health. A physician's strong warning to patients informing them of what we do know about the harmful effects of marijuana

may persuade some of them, especially those with marijuana-related symptoms, to quit smoking.

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Why Physicians Retire

To the Editor: The article on "Physicians' Adjustment to Retirement" in the February issue[1] misses the point. Show me one statement in the article that discusses the reasons physicians retire. Were the respondents reticent to reveal a reason, or were the authors avoiding exploring an obvious and deplorable reason?

There are many reasons physicians choose to retire: ambulatory difficulties, mental atrophy, loss of hearing or sight, and the like. The reason I found unconscionable, ruthless, and demeaning after 50 years in practice is the devastation of a noble profession into a meretricious business.

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* * *

Drs Virshup and Coombs Respond

To the Editor: Dr Tepper is concerned that we did not address the question of why physicians are retiring. We understand his position fully. We have written elsewhere that government intervention and control, skewed economic factors, and the emergence of health maintenance organizations (HMOs) have eroded medical ideals and ethics, physicians' sense of independence, and their sense of being special.[1] Medical employees of HMOs become gatekeepers, pushed to see more and more patients daily. Further stress has been added by the malignant threat of malpractice suits.

We agree with Dr Tepper that this is a climate in which many physicians are choosing to leave medicine and that we did not address this in our article.[2] What we did address was the fear of retirement itself. That, at least, we can deal with here—we and many others have been there. When the "whips and scorns" of practice become too great, retirement need not be viewed with alarm.

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A Fatal Case of Pulmonary Hemorrhage From Thoracentesis

To the Editor: Thoracentesis is frequently performed at the bedside and is generally considered to be "relatively uncomplicated technically, well-tolerated and quite safe."[1] We report a case that illustrates the danger of thoracentesis.

Report of a Case

The patient, a 96-year-old man, was admitted for cough and fever. He had been treated for pneumonia two weeks earlier at another hospital, but his symptoms failed to resolve. He had no history of abnormal bleeding. On admission his temperature was 38°C (101.3°F); examination elicited dullness to percussion and decreased breath sounds at the left base.

The patient had a leukocyte count of 6.5×10^9 per liter (0.87 neutrophils), a hemoglobin of 130 grams per liter, and a platelet count of 442×10^9 per liter. A chest x-ray film showed a right lower lobe infiltrate and a large left-sided pleural effusion that layered on the decubitus x-ray film.

He was admitted to hospital and remained febrile despite the intravenous administration of antibiotics. On the second hospital day, a left thoracentesis was done by a first-year and a third-year house officer. The effusion was percussed, and a 22-gauge needle was inserted 2 cm below the tip of the left scapula. No fluid was obtained, and the catheter-through-the-needle system was introduced into the same interspace. The catheter was advanced, again with no fluid collected. The procedure was halted and the patient placed back in bed. About three minutes later, the patient began to have gross hemoptysis and became unresponsive. Despite vigorous resuscitative measures, he died.

Postmortem examination revealed blood occluding the left main-stem bronchus and most of the proximal airways of the left lung as well as in the right main-stem bronchus and right lung; a 400-ml left hemothorax; two puncture marks on the posterior surface of the left lung; gross consolidation of the lower lung fields bilaterally; and a fibrinous exudate covering the left posterior lower aspect of the lung. The cause of death was recorded as hemoptysis due to needle puncture of the left lung during thoracentesis.

Discussion

In four prospective studies of thoracentesis involving a total of 404 patients in teaching hospitals, the incidence of pneumothorax ranged from 11% to 19% and of "dry tap" from 6% to 13%.[2-5] Serious complications such as splenic laceration, sheared-off catheter, and pneumohemothorax also occurred but were uncommon. Although many articles discuss dry taps and the use of the catheter-through-the-needle technique, we find only one other case of pulmonary hemorrhage as a complication of thoracentesis in the medical literature.[6] This involved a patient with dialysis-dependent renal failure, pneumonia, and a thoracentesis done with a 20-gauge spinal needle.

Our patient died of massive intrapulmonary hemorrhage due to catheter placement during a "dry tap." The risks and benefits of thoracentesis should be weighed carefully in each patient. Experienced personnel should supervise the procedure, and the catheter-through-the-

needle system should be used for therapeutic but not diagnostic procedures. The catheter should never be inserted if fluid is not obtained first with a conventional needle. Ultrasound guidance should be used in any difficult case and has been shown in one study to reduce the complication rate substantially.[5]

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No Time to Listen and Talk to Patients

To the Editor: The article by Lester and Smith, "Listening and Talking to Patients—A Remedy for Malpractice Suits?" in the March issue examines the way physicians communicate with patients and how good communication seems to improve the physician-patient relationship, making malpractice suits less likely.[1] What is not included in this article, but what must also be made clear, is the effect that the current reimbursement climate has on the physician-patient relationship. For those of us in private practice, reimbursement continues to be cut. Physicians are forced to see more patients. If the physician extends office hours to do so, this will certainly increase fatigue and affect the manner in which physicians interact with patients. For those whose office hours are already set to the limit, more patients will have to be seen in the same amount of time, affording less time for each patient.

New payment policies based on revised American Medical Association Evaluation and Management Codes specify that services are to be "problem-focused." Whereas in the past physicians have cultivated their relationships with patients by sometimes spending time in what might be construed as idle chatter, this now becomes a waste of potentially important, income-related time.

Some might say that, regardless of payment regulations, physicians are still expected to establish the same relationships with patients that they had 20 years ago. I, on the other hand, think it is more realistic to note that society's obligation toward physicians has certainly changed over the past 20 years, and it is only logical to expect the physician-patient relationship to change as well.

Perhaps we may read in the future how the nurse practitioner or physician assistant's interaction with patients is important in avoiding lawsuits, because I foresee managed care experts realizing that these health care workers are a lot cheaper to employ as gatekeepers than are physicians.

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The Editors are pleased to receive letters commenting on articles published in the journal in the past six months, as well as information or short case reports of interest to our readers. ALL MATERIAL SUBMITTED FOR CONSIDERATION MUST BE DOUBLE-SPACED. Letters NO LONGER THAN 500 WORDS are preferred. An original typescript and one copy should be submitted. All letters are published at the discretion of the Editors and subject to appropriate editing. Those of a scientific nature will be peer reviewed. Authors should include information regarding conflict of interest, when appropriate ("I warrant that I have no financial interest in the drugs, devices, or procedures described in this letter"). Most letters regarding a previously published article will be sent to the authors of the article for comment. Authors of accepted letters will have an opportunity to review the edited version before publication.

Lessons From the Practice

What Is Medicine All About?

HAROLD J. FORNEY, MD, *La Jolla, California*

During 28 years of orthopedic practice, I have had plenty of opportunity to speculate on the question, what is medicine all about?

Let me tell you about Jessica, age 6. She and her younger brother had chickenpox, usually a benign childhood disease. Unfortunately, Jessica became secondarily infected with a *Staphylococcus* species, with resultant septicemia and toxic shock syndrome. By the time I saw her on her 18th day in the intensive care unit, she had suffered cardiac arrest, respiratory failure, renal failure, liver failure, and gangrene of all four extremities. I was called to consult because of my interest in amputations and prosthetics.

A pitiful little thing, Jessica was lying in bed under total sedation, connected to a multitude of tubes and monitors, her thin arms and legs completely black and mummified, with early demarcation. No one knew if she would survive, but it was obvious that she would need all four limbs amputated. After I had several lengthy and very tender counseling sessions with Jessica and her parents, she underwent the amputations in stages, with subsequent skin grafts designed to preserve as much limb length as possible.

Miraculously, she began to regain all of her vital functions. She had two or three setbacks because of osteomyelitis that had to be drained, but otherwise her progress was steady and rapid. She had absolutely no brain damage and began occupational and physical therapy even before the wounds were healed. She was fitted with below-elbow, body-powered prostheses, and within half an hour, she had so mastered the control moves that she could transport a piece of bacon to her mouth with the terminal hook.

A few days later, Jessica was visited by a 12-year-old girl from a nearby city who had undergone similar surgical procedures two years before. The two girls hit it off immediately. Jessica was all eyes as she watched the older girl open a container of lip gloss and then explain all the other things she was able to do with her prostheses. The two hours I spent with these two families were some of the most rewarding of my entire medical career.

It has been more than two years now since Jessica's operations, and I have had the opportunity to follow her rehabilitation on a regular basis. She is an absolutely charming little girl. She is keeping up with her class in school with no trouble. She rides her bicycle (with training wheels), plans on taking horseback riding during her next school break, and wants to resume her dancing lessons, an activity she really enjoyed before her illness. She also maintains a heavy schedule of public appearances. She is in great demand by hospitals, the Easter Seals organization, the blood bank, and other agencies.

Recently I arranged for Jessica to meet Paul, a 56-year-old man who had undergone a complete hemicorpectomy for cancer two years ago. He had gone through a period of depression immediately after his operation, but seeing Jessica on television gave him the courage and inspiration to go on with his rehabilitation. Paul was now functioning in his wheelchair and beginning to use his prostheses. The instant bonding that took place between these two was nothing short of miraculous. They discussed their functional abilities in a totally relaxed and uninhibited manner. They agreed that when they died and went to heaven, God would give them back their missing limbs. As I watched them, I once again realized how modern medical technology followed by intensive rehabilitation had worked for these two people. *This* is what medicine is all about.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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(Forney HJ: What is medicine all about? West J Med 1993; 158:640)

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On Not Overlooking the Obvious

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The ward resident paused outside the door. "This next patient is an asthmatic who has been on a standard regimen of several medicines, including steroids, and is in for her ninth admission in the past two years. She has been intubated three times. She keeps forgetting her medicines; we have wondered about compliance on a number of occasions. She came in last night with a Po_2 of 50. She was put on nasal oxygen and given bronchodilators, steroids, and antibiotics. She is better this morning. Why don't we move on to the next patient, who presents a quite interesting problem?"

"Let's talk to this patient for just a moment," said the attending physician.

"Mrs Jones, I am Dr Smith. I work with the house staff physicians who are taking care of you, and would like to ask you a few questions. I understand you are feeling better this morning?"

The patient nodded.

"We only have a few minutes. I don't really know too much about you or your asthma. Can you tell me why you had to come to the hospital last night?"

"I ran out of medicine."

"You ran out of medicine?"

"Yes, I forgot to get my prescriptions refilled at the pharmacy. I got more and more short of breath and had to come to the emergency room."

"Mrs Jones, you have been intubated two or three times before, is that correct?"

The patient nodded.

"It is uncomfortable being intubated, isn't it?"

The patient nodded vigorously.

"What I cannot understand, Mrs Jones, is how you could allow yourself to run out of medicines knowing that your asthma might get worse and that you would be intubated again. The patients I have cared for who have previously been intubated would do anything in their power to avoid it again. What is going on in your life that makes it different for you?"

A tear appeared in the patient's eye. Then she revealed that both she and her son by a previous marriage were being physically abused by a live-in boyfriend. Her only way of mitigating family violence was to become so ill that the family had to bring her to the hospital for treatment. The patient knew she could bring on her asthma only by discontinuing her medications.

After another hospital stay several months later, Mrs Jones began family therapy and counseling and has not been admitted to hospital for over a year.

* * *

"Lessons From the Practice" presents a personal experience of practicing physicians, residents, and medical students that made a lasting impression on the author. These pieces will speak to the art of medicine and to the primary goals of medical practice—to heal and to care for others. Physicians interested in contributing to the series are encouraged to submit their "lessons" to the series' editors.

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(Blossom HJ: On not overlooking the obvious. West J Med 1993; 158:641)

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Lawrence D. Dorr, M.D., *director of the Center for Arthritis and Joint Implant Surgery at USC University Hospital, and professor of Orthopaedic Surgery at the University of Southern California School of Medicine, is a leader in joint replacement research, authoring more than 100 scientific articles. He has extensive surgical experience in joint replacement, which includes 2,500 hip and knee replacements in the past decade alone. He was named in the text of "Best Doctors in America" for 1992-1993.*

Dr. Dorr was the designer for the APR hip system, a pioneer in bone ingrowth fixation. He also designed the Apollo Hip and Knee Systems, which are modern cemented implants designed for economical longevity.

Edward J. McPherson, M.D., *assistant professor of Orthopaedic Surgery at the University of Southern California School of Medicine, is a member of the Center for Arthritis and Joint Implant Surgery at USC University Hospital. Dr. McPherson will head the revision service at the Center.*

Dr. McPherson's research interests include hip pain in athletes, the study of surface coatings to enhance bone ingrowth fixation in hip and knee replacements, and the study of articular surface coatings to reduce friction and wear. Additionally, Dr. McPherson has specialized interest and training in revision arthroplasty of the hip and knee, as well as experience with reconstruction and replacement of the shoulder and elbow.

Desmond M. Dall, M.D., F.R.C.S., *professor of Clinical Orthopaedics at the University of Southern California School of Medicine, is a member of the Center for Arthritis and Joint Implant Surgery at USC University Hospital.*

Dr. Dall has several major areas of research interest, including reconstructive surgery of the hip and knee, comparative functional evaluation of different antero-lateral approaches to the hip joint in total hip replacements, and the effect of muscular activity on the hip and endoprosthesis fixation. He also is investigating new fixation techniques in high tibial osteotomy and development of new techniques of internal fixation of long bones.

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NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

September 10-11—**New Mexico Chapter, American College of Surgeons Annual Meeting.** Holiday Inn Pyramid, Albuquerque. Fri-Sat. Contact: Bonnie Smith, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 269-5883 or (505) 828-0237.

October 1-2—**John N. Wilson, MD, Lectureship in Cardiology: Cardiology '93.** Albuquerque Hilton Hotel. Fri-Sat. Contact: Mary Boning, PO Box 26666, Albuquerque 87125-6666. (505) 841-1225.

October 16—**New Mexico Orthopaedic Association Annual Meeting: Sports Medicine.** Inn at Loretto, Santa Fe. Sat. Contact: Elsa Hall, 7770 Jefferson NE, #400, Albuquerque 87109. (505) 828-0237.

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UNM SOM—University of New Mexico School of Medicine, Office of CME, PO Box 713, Albuquerque 87131. (505) 277-3942.

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July 5-9—**Update in Internal Medicine.** UUSM at Olympia Hotel and Conference Center, Park City. Mon-Fri. Contact: UUSM.

July 29-31—**Summer Shakespearean Meeting.** Cedar City. Thurs-Sat. Contact: UOS.

September 22-25—**Utah Medical Association Annual Meeting.** University Park Hotel, Salt Lake City. Wed-Sat. Contact: UMA, 540 E Fifth South, Salt Lake City 84102. (801) 355-7477.

MEDICAL GRAND ROUNDS

Weekly—Internal Medicine Grand Rounds, Psychiatry Grand Rounds, OB/GYN Grand Rounds, Pediatric Grand Rounds. Contact: UUSM, Office of CME, (801) 581-8664.

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CS: Charter Summit Hospital, 175 W 7200 South, Midvale 84047. (801) 561-8181.
DM: Dixie Medical Center, 544 S 400 East, St George 84770. (801) 634-4000.
ETS: Emergency Training Services, 777 N 390 East, American Fork 84003. (801) 763-3555.
FHP: FHP of Utah, 35 W Broadway, Salt Lake City 84101. (801) 355-1234.
ITS: Intermountain Thoracic Society, 1616 S 11th East, Salt Lake City 84105. (801) 484-4456.
LDSH: LDS Hospital, 8th Ave and "C" St, Salt Lake City 84143. (801) 321-1100.
LRH: Logan Regional Hospital, 1400 N 5th East, Logan 84321. (801) 752-2050.
MVH: Mountain View Hospital, 1000 E Highway 6, Payson 84651. (801) 465-9201.
OSS: Ogden Surgical-Medical Society, PO Box 9311, Ogden 84409.
PCMC: Primary Children's Medical Center, 100 N Medical Dr, Salt Lake City 84113. (801) 588-2000.
PVH: Pioneer Valley Hospital, 3460 S 4155 West, West Valley City 84120. (801) 968-9061.
UMIA: Utah Medical Insurance Association, 540 E 500 South, Salt Lake City 84102. (801) 531-0375.
UOS: Utah Ophthalmological Society, 540 E 500 South, Salt Lake City 84102. (801) 355-7477.
USH: Utah State Hospital, PO Box 270, Provo 84603-0270. (801) 373-4400.
UUSM: University of Utah School of Medicine, Office of Continuing Medical Education, 50 N Medical Dr, Salt Lake City 84132. (801) 581-8664.
VAMC: Veterans Administration Medical Center, 500 Foothill Dr, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

The listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here, please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 441-WSMA.

Brochures and registration forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 19—**Medical Malpractice: Biennial Update.** Seattle. Sat. Contact: U/W.

June 21-22—**ACLS.** Tacoma. Mon-Tues. Contact: PCMS CME.

June 25—**Family Medicine Day—Hypertension.** Tacoma. Fri. Contact: Multicare. (206) 592-1221.

June 25-26—**Osteoporosis.** Seattle. Fri-Sat. Contact: U/W.

July 9—**Update From the IXth International AIDS Conference in Berlin, Germany.** Seattle. Fri. Contact: U/W.

July 16—**AIDS Update: A Primary Look.** Renton. Fri. Contact: VMC. (206) 228-3440.

August 2-7—**Summer Seminar in Health Care Ethics.** Seattle. Mon-Sat. Contact: U/W.

August 15-18—**Oncology.** Everett. Sun-Wed. Contact: PNMEII. (206) 258-6322.

August 27-28—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital. (206) 526-2501.

September 9-12—**Washington State Medical Association Annual Meeting and Scientific Session.** Jantzen Beach, Oregon. Thurs-Sun. Contact: WSMA.

September 10—**Emergency Physicians Scientific Session.** Jantzen Beach. Fri. Contact: WACEP, (206) 441-9762.

September 11—**Ophthalmology Scientific Session.** Jantzen Beach. Sat. Contact: WAEPS, (206) 441-9762.

September 13-17—**21st Annual Advances in Family Practice.** Seattle. Mon-Fri. Contact: U/W.

September 17-18—**Children's Orthopedic Conference.** Seattle. Fri-Sat. Contact: Children's Hospital. (206) 526-2501.

September 22-25—**North Pacific Pediatric Society.** Vancouver, BC. Wed-Sat. Contact: Children's. (206) 258-6322.

September 23—**Domestic Violence.** Everett. Thurs. Contact: PNMEII, (206) 258-6322.

October 1—**Pharmacology.** Tacoma. Fri. Contact: Multicare, (206) 522-1221.

October 8-9—**Society for Pediatric Pathology.** Seattle. Wed-Fri. Contact: Children's Hospital, (206) 526-2501.

October 15—**The Walking Wounded—Acute Care Outside the ICU.** Everett. Fri. Contact: PNMEII, (206) 258-6322.

October 22-23—**Adolescent Medicine.** Seattle. Thurs-Fri. Contact: Children's Hospital, (206) 526-2501.

October 23—**Pediatric Endocrinology.** Tacoma. Fri. Contact: Multicare, (206) 522-1221.

October 27—**Perinatology Conference.** Tacoma. Wed. Contact: Multicare, (206) 552-1221.

November 4-5—**Drug Therapy.** Seattle. Thurs-Fri. Contact: U/W.

(Continued on Page 656)

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1993-94 FALL/WINTER SERIES HIGHLIGHTS

JULY 1993

1. 29th Annual Internal Medicine Program
   July 18-23, 1993 Estes Park, CO
2. 20th Annual Renal Disease Program
   July 26-30, 1993 Given Institute, Aspen, CO
3. 2nd Annual Medical Ethics Conference
   July 30 - August 1, 1993 Given Institute, Aspen, CO

AUGUST 1993

4. 17th Annual Dynamic Psychotherapy Program
   August 2-6, 1993 Given Institute, Aspen, CO
5. 36th Annual Pediatric Program
   August 8-12, 1993 Given Institute, Aspen, CO
6. Diagnosis & Treatment of Perinatal Arrhythmias
   August 13-15, 1993 Aspen, CO
7. 3rd Annual Musculoskeletal Infection Society Meeting
   August 20-21, 1993 Snowmass Village, CO
8. 18th Annual Primary Musculoskeletal Care Program
   August 23-28, 1993 Breckenridge, CO

NOVEMBER 1993

9. 39th Annual Family Practice Review
   November 8-12, 1993 Denver, CO

DECEMBER 1993

10. Practical Issues in Infectious Diseases: Bugs & Drugs in the '90s
    December 10-11, 1993 Denver, CO

JANUARY 1994

11. Reconstructive Surgery of the Hip and Knee
    January 22-29, 1994 Steamboat Springs, CO
12. Contemporary Management of Unstable Coronary Syndromes
    January 27-29, 1994 Breckenridge, CO

FEBRUARY 1994

13. The Colorado Conference on the Family Practice
    January 30 - February 4, 1994 Denver/Breckenridge, CO

MARCH 1994

14. Horizons in Surgery
    February 26 - March 5, 1994 Breckenridge, CO
15. Colorado Review of Anesthesia
    February 26 - March 4, 1994 Vail, CO

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CMA's Department of Physician Education has produced a new CME program, "HIV Risk Assessment: Methods and Guidelines," which is available free to physicians. This program teaches effective strategies developed by expert physicians to identify patients who are potentially at risk for HIV infection. Worth one hour of CME Category I credit, the program is designed for groups of 5-20 physicians.

The program features CMA's award-winning, 11-minute video, "Let's Talk," which highlights several methods physicians can use to perform HIV assessment with patients. Participants receive a course outline, camera-ready slide reproductions, a compilation of state laws pertaining to HIV/AIDS, community resource guide to HIV testing and counseling, risk assessment guidelines, and a model HIV consent form and patient information pamphlet.

Those interested in taking part in this unique CME program should contact Amy Wright in CMA's Department of Physician Education at 415/882-5186.

LET'S TALK
ABOUT AIDS RISK

CONTINUING MEDICAL EDUCATION

(Continued from Page 654)

November 18-19—**Regional Musculoskeletal Conference.** Seattle. Thurs-Fri. Contact: U/W.

November 19—**Advances in Therapeutics for the Clinician.** Renton. Fri. Contact: VMC, (206) 228-3440.

December 2-4—**American College of Physicians.** Seattle. Thurs-Sat. Contact: U/W.

December 9-12—**9th Infectious Disease Conference.** Everett. Tues-Sat. Contact: PNMEH, (206) 258-6322.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

PCMS CME—Contact: Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

WSMA—Washington State Medical Association, Continuing Medical Education, 2033 Sixth Ave, Suite 900, Seattle, WA 98121. (206) 441-9762.

WYOMING

June 10-12—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Thurs-Sat.

October 29-30—**16th Annual Perinatal Conference.** Children's Hospital of Denver at Laramie. Fri-Sat. Contact: Conference Office, (303) 861-6946 or (800) 225-0010. ◆

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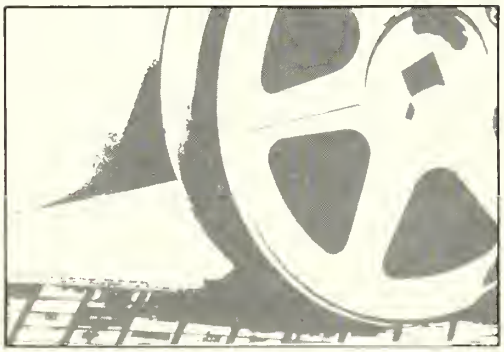

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(Continued on Page 659)

(Continued from Page 658)

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NORTHERN CALIFORNIA. Opportunities available with Comprehensive Medical Evaluations in Sacramento, San Jose, and Monterey bay area for BC physicians in Orthopedic Surgery, Psychiatry, Internal Medicine, and subspecialties, Dermatology, Neurology, Physical Medicine/Rehabilitation, Ophthalmology, Otolaryngology, Plastic/Reconstructive Surgery and Toxicology/Occupational Medicine, to perform forensic medical evaluations. This is an excellent opportunity to supplement income without increasing your practice overhead. Send inquiry to Terence Doyle, Comprehensive Medical Evaluations, 87 Scripps Dr, Ste 308, Sacramento, CA 95825; or call (916) 567-3411.

MEDICAL DIRECTOR. Monterey Bay 230-bed hospital in the heart of Steinbeck country is actively seeking an MD interested in a management role as the administration liaison to the medical staff. Requirements include proven communication skills, minimum five years clinical practice experience, working knowledge of managed care contracting, governmental regulations, UR/QA, credentialing, and planning. If you are a team player with the desire and ability to lead a quality medical staff into the '90s, contact Ken Baker, Baker Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111; (800) 229-0411 or FAX (415) 399-0411.

PHYSICIANS LOOKING FOR PHYSICIANS. Find the right MD for your practice. Place a classified advertisement in The Western Journal of Medicine. See the ad order blank for details or call (415) 882-3376 for more information.

(Continued on Page 661)

(Continued from Page 660)

PHYSICIANS WANTED

KAISER PERMANENTE

Good People Good Medicine

NORTHERN CALIFORNIA

Several positions available for Internal Medicine, most medical subspecialties, ENT, Orthopedics, Anesthesiology, and OB/GYN. We are a young, aggressive group in a well known prepaid group practice HMO organization with excellent benefits and a very reasonable call schedule. You will have a rewarding practice opportunity with ample time to enjoy the mountains and San Francisco which are nearby. If interested please call or send CV to Physician Recruitment, Administration, The Permanente Medical Group, Inc, 1305 Tommydon St, Stockton, CA 95210; (209) 476-3300.

ROCKY MOUNTAIN WEST AND SOUTHWEST NEED PHYSICIANS. All specialties needed. Urban, rural, solo, group opportunities, all close to mountain recreation. Call Rita Longino at (800) 279-5267 or FAX CV to (800) 467-1246 or send CV to WHS, PO Box 2107, Corrales, NM 87048-2107.

NORTHERN CALIFORNIA RECREATION AREA. Multispecialty group has immediate opening for an Internal Medicine practitioner with a particular interest in Critical Care. Clinical activities involve full range of Internal Medicine outpatient and inpatient practice. Beautiful northern California location offers abundant recreational opportunities as well as small town living. Competitive salary and comprehensive benefit package. Please send CV to 10978 Donner Pass Rd, Truckee, CA 96161.

ASSOCIATE IN PEDIATRICS. Kern Medical Center, Bakersfield, California, a teaching hospital affiliated with UCLA and UCI Schools of Medicine, seeks an Associate in the Division of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in UCLA Department of Pediatrics. Comprehensive salary and benefit package. A part-time private practice is permitted. Medical center is in central California, a mid-sized urban community with moderate cost of living. Send CV and inquiries to Navin Amin, MD, Chairman, Department of Family Practice/Pediatrics, Kern Medical Center, 1830 Flower St, Bakersfield, CA 93305.

OPPORTUNITY–URGENT CARE AND FAMILY PRACTICE. Work, live, and play within minutes of any outdoor activities you ever dreamed of. Boise offers it all including culture and an excellent atmosphere for family living. Choose 12 or 24 hour shifts. Be able to have three and four days off in a row. No on-call duties. Work at one, two, or each of our multiple facilities covering Emergency Rooms and Walk-in Family Practice. Contact Janet Meyers at (208) 323-1223 or write 2153 Century Wy, Boise, ID 83709 to learn more about our new, exciting benefit package. (Positions also available in New Mexico.)

INTERNAL MEDICINE/PRIMARY CARE. BC/BE, recently trained (university program preferred) for group practice in San Francisco. Send CV and availability to A. Aronow, MD, 45 Castro St, San Francisco, CA 94114.

Moving Ahead in '93!

The California Department of Corrections has a number of opportunities available in the following areas:

DEPARTMENT OF CORRECTIONS CALIFORNIA

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PHYSICIANS

Program Manager - Chief Medical Officer

Infectious Disease Unit - Sacramento

This is the Lead Manager Position for statewide HIV-TB program administration and HIV-ID Training for the entire department.

Medical Consultant - Physician

Internal Medicine - Primary Care - General Practice - Family Practice - Madera, Chino, Tehachapi, Tracy, Ione, Crescent City, Corcoran, San Diego, Wasco, San Luis Obispo, Norco, Folsom, San Quentin, Calipatria, Lancaster, Delano, Susanville

Positions are flexible: full-time, part-time and contract consultant.

Competitive Salary - Excellent Benefits

For any of the above opportunities, call (916) 327-7081.

Or send Curriculum Vitae to: California Department of Corrections, Dept. DHCS, P.O. Box 942883, Sacramento, CA 94283-0001. Fax (916) 322-5864 EOE.

PHYSICIANS WANTED

FAMILY PHYSICIAN–LEWISTON, IDAHO

Opportunity to join Family Practice group. Ambulatory and acute/inpatient care. No OB. Competitive income guarantee with opportunity to join full partnership. Send CV to Clearwater Medical Clinic, 1522 17th St, Lewiston, ID 83501, attn: Peggy Johnson, or call (208) 743-8416.

FAMILY PRACTICE PHYSICIAN. Full-time in a busy walk-in medical clinic. Located in Visalia, California (Tulare County). Malpractice insurance, good salary, etc. Please call (209) 627-5555 for more information.

HAWAII. FAMILY PRACTITIONER needed for rural Oahu. Full-time position in nonprofit community health center. Desire dedication to work in multicultural setting. Obstetric skills preferred. Send letter and CV to Puanani Kalawa, Waianae Coast Comprehensive Health Center, 86-260 Farrington Highway, Waianae, HI 96792; (808) 696-7081.

EXCELLENT OPPORTUNITY for physician practicing Internal Medicine to join three doctor-established practice in Marin County. Compensation negotiable and partnership opportunity. Respond to Internal Medicine, Ste 200, 1300 S Eliseo Dr, Greenbrae, CA 94904.

MONTEREY BAY. Midway between Santa Cruz and Monterey, this unpretentious community is perfect for the hiker, biker, surfer, and outdoorsperson. Medical staff is anxious to welcome additional BE/BC physicians in Family Practice and Pediatrics. Group and independent practice with call schedule which allow time for lifestyle. Contact Physician Search Group, 550 Montgomery St, Ste 725, San Francisco, CA 94111, (800) 229-0411 or FAX (415) 399-0411.

PHYSICIANS WANTED

HCR

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Ste 201-B
PO Box 1221
Bend, OR
97709
(800) 323-1732
(503) 382-1732

ORTHOPEDIC SURGEON

Valley Medical Center of Fresno, a Primary teaching hospital for the University of California, San Francisco–Fresno Medical Education Program, seeks a BC/BE Orthopedic Surgeon to fill a faculty/staff position. Eligibility for a UCSF academic clinical appointment preferred. The Orthopedic Department at VMC supports a busy level one trauma center and actively participates in teaching residents in General Surgery, Emergency Medicine, and Family Practice. Competitive salary and benefits. Central California location offers enjoyable and affordable year-round recreational living with easy mountain and coastal access.

Address inquiries to **Richard A. Lockwood, MD, Assistant Dean/Director of Medical Affairs, 445 S Cedar, Fresno, CA 93702. Equal opportunity employer; women and minorities are encouraged to apply.**

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PHYSICIANS WANTED

PACIFIC NORTHWEST OPPORTUNITIES

• INTERNISTS • PEDIATRICIANS • FAMILY PHYSICIANS

Northwest Permanente, P.C., is seeking a Board Certified or Eligible Internist, Pediatrician or Family Physician to cover the clinical practice of physician colleagues who are on sabbatical, parental leave, or other long-term leave. Our multi-specialty group is comprised of 540 physicians who provide a full range of services to 380,000 members of Kaiser Permanente in primarily the Portland metropolitan area. We have two full-service hospitals and 11 primary care clinics in addition to six other clinics in the region.

Northwest Permanente offers a professionally stimulating environment and a competitive salary/benefit package which includes professional liability coverage, family medical/dental insurance, two pension programs, and other benefits. **For more information, please contact Judy Parmenter, Professional Staff Recruiter at (503) 721-3874, or forward inquiry with C.V. to: W. J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Ste. 300, Portland, OR 97210-5398. EOE.**

KAISER PERMANENTE
Northwest Permanente, P.C.
Physicians and Surgeons

MIDWEST

Family centered community in lakes region of northeast Indiana, 25 miles from Fort Wayne, seeks additional BE/BC Family Practitioner. Modern, full service, waterfront hospital had operating revenues of $20 million last year and saw 10% growth in all subspecialties. This facility has the second largest home health care department in the state which exceeded 100,000 visits last year. Enjoy many rural and urban activities with access to nearby universities. $105,000 income guarantee plus $20,000 sign-on bonus, all benefits and overhead. Call 1:6. **Call Cheryl Broderick at (800) 762-9213.**

OPPORTUNITY. BC physician (Family Practice, Internal Medicine, or Occupational Medicine) for a busy private/industrial medicine practice in Los Angeles. Bilingual preferred (medical Spanish required). Clinic is affiliated with a major medical center. Excellent salary. Send CV to Number 281, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602

ENJOY THE GREAT SOUTHWEST. Thomas-Davis Medical Centers, an expanding multispecialty group of 190 plus physicians, needs BC/BE Pediatrics, Internal Medicine, Family Practice, OB/GYN, Urgent Care, Urology, General Surgery, Psychiatry, and Hematology/ Oncology physicians. Top benefits, profit sharing, guarantee first two years, plus incentive pay, early shareholder. Fee-for-service plus HMO. Call or write TDMC/CPR, (800) 658-9166, TDMC, PO Box 12650, Tucson, AZ 85732.

INTERNIST/FAMILY PRACTICE. Physicians for well loved multidisciplinary Geriatric health center. Part of east San Francisco bay area community clinic network. Permanent and locum tenens positions available. 50-80% time. Participation in hospital and call coverage desired. Resident teaching and UCSF clinical affiliation possible. Call (510) 644-6060.

MAJESTIC SKAGIT VALLEY IN WESTERN WASHINGTON has multispecialty group seeking eighth Family Practitioner. BC/BE, OB optional. Competitive salary and benefits. If interested, send CV to Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

OB/GYN. Multispecialty group in northwest Washington desires second Obstetrician. Excellent practice opportunity, full range of benefits, early partnership status, all practice costs paid. For more information contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273; (206) 428-2524

PHYSICIANS–Do you want to purchase a practice? Check the Practices Available section at the end of the classifieds.

PHYSICIANS WANTED

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HOLY FAMILY HOSPITAL and the MEDICAL STAFF are working together to meet the healthcare demands of our 150,000 patient population. There is an IMMEDIATE need for BC/BE physicians in the following specialties:

- FAMILY PRACTICE
- PEDIATRICS
- INTERNAL MEDICINE
- ORTHOPEDICS

SPOKANE, WASHINGTON (370K metro population) is the regional Healthcare and Cultural center offering a sound economy, unlimited outdoor recreation and a mild four season climate.

CONTACT with CV to: **Nancy Chaffins**

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SPOKANE, WA 99207
(509) 482-2164
FAX: (509) 482-2187

ARIZONA. Hospital sponsored solo opportunities for Family Practitioners and Internists. Excellent compensation with ample coverage. Well-equipped facility including MRI and CT. Send CV or contact Mitch Young, PO Box 1804, Scottsdale, AZ 85252; (602) 990-8080; FAX (602) 990-8513.

SALT LAKE CITY–URGENT CARE/FAMILY PRACTICE. Six year old center in upper middle class community. BC preferred, early partnership available. Great recreation area. Work Net, PO Box 26692, Salt Lake City, UT 84199.

MONTEREY, CALIFORNIA. BC/BE Internist needed to replace retiring partner in busy four member group. Reply to Number 273, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602

PUGET SOUND–WASHINGTON STATE. OB/GYN independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

PUGET SOUND–WASHINGTON STATE. ENT independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

(Continued on Page 663)

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PHYSICIANS WANTED

INTERNAL MEDICINE

LONGVIEW-KELSO, WA

NORTHWEST PERMANENTE, P.C., has two excellent opportunities for Board Certified or Eligible General Internists to join our 16-physician primary care group in Longview-Kelso, Washington, a picturesque, stable community of 42,000 people. A full range of professional services are provided to Kaiser Permanente's 26,000 plan members in the area.

We offer a competitive salary and benefit package which includes two comprehensive pension plans, paid professional liability and sabbatical leave. **Forward C.V. and inquiry to: W.J. Weiland, M.D., Regional Medical Director, NORTHWEST PERMANENTE, P.C., 2701 N.W. Vaughn St., Ste. 300, Portland, OR 97210-5398. EOE.**

KAISER PERMANENTE
Northwest Permanente P.C.
Physicians and Surgeons

Western States OPENINGS

Many multispecialty groups and hospitals have asked us to recruit for over 300 positions of various specialties. Both permanent and locum tenens. Send CV to **Western States Physician Services, 5627 E. Kings Canyon, Ste 156, Fresno, CA 93727, or call 1 (800) 873-0786.**

BC/BE FAMILY PHYSICIAN to join five physician, two mid-three, mid-level (three Family Practitioners, one OB, one Internal Medicine, one Certified Nurse Midwife, two Physician's Assistants) busy migrant/community clinic in Grandview, Washington. Full-range Family Practice, including Obstetrics, hospital work and Emergency Room coverage. Excellent relationship with well trained BC Family Practitioners and Surgeon in community. Friendly rural area with good schools. Close to mountain recreational areas and water sports. Professional liability paid. Excellent benefits, vacation up to 32 days per year. Public Health Service immediate loan repayment slot. Contact Ann Garza, Director of Personnel, or Sylvan Robb, Recruiting Specialist, Yakima Valley Farm Workers Clinic, PO Box 190, Toppenish, WA 98948; (509) 865-5898.

OUTSTANDING OPPORTUNITY for BC/BE physician to join busy, stable practice in Internal Medicine in magnificent Napa Valley. Send CV and correspondence to Number 279, Western Journal of Medicine, PO Box 7602, San Francisco, CA 94120-7602.

(Continued on Page 664)

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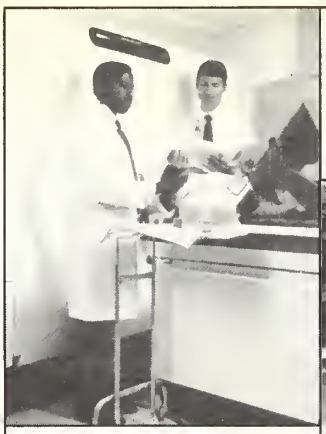

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"Now that I'm practicing with CIGNA Healthplan, I have more time to spend with my son...I'm even coaching his swimming team this year."

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- Orthopaedic Surgeon
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- Rheumatologist
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ARIZONA
Phoenix

- Anesthesiologist
- Family Physicians
- General/Vascular Surgeon
- General Internists
- Geriatric Internists
- Invasive Cardiologist
- OB/Gyns
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California: CIGNA Healthplans of CA, Physician Recruitment, 505 N. Brand Blvd., Suite 400-49, Glendale, CA 91203, (800) 468-9013.

Arizona: CIGNA Healthplan of AZ, Physician Recruitment, 11001 N. Black Canyon Hwy, Suite 400-49, Phoenix, AZ 85029, (800) 252-2471.

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PHYSICIANS WANTED

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Get into Private Practice with UHS From Coast-To-Coast

We have a network of Private Practice Opportunities with established physicians or groups in the following areas.

Excellent financial packages plus incentives make these outstanding opportunities to explore.

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- OB/GYN, PEDIATRICS
- PULMONARY MEDICINE

WASHINGTON
- GASTROENTEROLOGY
- FAMILY PRACTICE
- OB/GYN

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FAX: (817) 927-0030

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(510) 204-4624 or (510) 204-4536

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Immediate opportunities for BC/BE physicians in Southern, Northern, and Central California, Family Practice, Internal Medicine, OB/GYN, Pediatrics, Orthopedics, Hematologist/Oncologist, Pediatrics/Surgery, and Physician Assistants.

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2170 Century Park East, #806
Los Angeles, CA 90067
Or Call
(310) 556-2126, FAX (310) 556-1604

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OTOLARYNGOLOGIST. BC/BE to join 28 physician multispecialty group practice. Located in beautiful Pacific northwest between Seattle and Vancouver, BC. Contact Shane Spray, 1400 E Kincaid, Mount Vernon, WA 98273.

WE VALUE YOUR SKILLS IN THE PACIFIC NORTHWEST. Do you practice Obstetrics? Have Spanish language skills? Do you enjoy working with underserved populations? Community and migrant health centers in Alaska, Idaho, Oregon, and Washington have diverse opportunities for Family Physicians in urban and rural areas, some including loan repayment. Practice where it's nearly perfect. Send CV to NWRPCA, 4154 California Ave SW, #7, Seattle, WA 98116, (206) 932-2133.

SAN FRANCISCO BAY AREA. PALO ALTO MEDICAL CLINIC, a 150 physician multispecialty group noted for innovation and excellence seeks full-time physician for Occupational Medicine practice. Physicians with BC in Occupational Medicine, Family Practice, or Emergency Medicine preferred. Practice environment, salary, and benefits are unexcelled. Two year partnership track. Please forward letter of interest and résumé to George Perlstein, MD, Medical Director, Palo Alto Medical Clinic, 300 Homer Ave, Palo Alto, CA 94301.

CALIFORNIA. IME, QME, AMEs, Orthopedists, and Neurologists for established office in central/northern California. Excellent terms, flexible hours. Medical Specialists of California; (800) 606-9800.

PHYSICIANS WANTED

FAMILY PRACTICE. Premier multispecialty group near Portland, Oregon has two excellent opportunities for BC/BE Family Practitioners. Join one of two satellite clinics in which Family Physicians and Physician Assistants currently practice. Superb lifestyle, abundant recreational opportunities, and generous benefits package. Send CV to Karen Stanton, c/o The Vancouver Clinic, 700 NE 87th Ave, Vancouver, WA 98664.

EMERGENCY MEDICINE UNIVERSITY POSITION. The University of California, Davis, School of Medicine, is recruiting for a full-time faculty member. The position will be at the Assistant or Associate Professor level. The Division of Emergency Medicine and Clinical Toxicology is undergoing rapid academic development and has an approved residency program in Emergency Medicine. The UCDMC Emergency Department provides comprehensive emergency service and is a major trauma center in northern California. The Department is a paramedic base station and training center, and in addition, has an active helicopter service and regional poison center. Candidates must be BC/BE in Emergency Medicine and be eligible for licensure in California. A letter outlining teaching background, interests, experience, and research in addition to a CV and the names of five references should be sent to Robert W. Derlet, MD, Chair, Emergency Medicine Search Committee, Tr 1219, University of California, Davis, Medical Center, 2315 Stockton Blvd, Sacramento, CA 95817. Applications will not be accepted after July 1, 1993. The University of California is an Affirmative Action/Equal Opportunity Employer.

ORTHOPEDIC SURGEONS. Orthopedic Surgeon for a very busy Orthopedic service in a 223-bed teaching hospital with residencies in General Surgery, Internal Medicine, OB/GYN, and Family Practice. Should be BC/BE. Experience in arthroscopy preferred. Salary and compensation plan negotiable depending on experience. Hospital located in beautiful northern San Joaquin Valley close to major cities and skiing areas. Please submit CV and references or contact Nathaniel Matolo, MD, Chief of Surgery, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; phone (209) 468-6600. AA/EOE.

NORTHERN CALIFORNIA HOSPITAL seeking a BC/BE Internist to staff its new satellite medical clinics. Assistance is available in establishing a practice. Net income guarantees are open including support for office staff and required equipment. Contact Margaret Ward, Redbud Community Hospital, PO Box 6720, Clearlake, CA 95422; (707) 994-6486, ext 128.

FLORIDA GULF COAST. Two BC Hematologists/Oncologists seeking third to join pure subspecialty practice. Competitive salary and excellent benefits. ECOG, GOG. Sophisticated medical community with a tropical climate. Send CV with cover letter to Practice Manager, 306 South Blvd, Ste B, Tampa, FL 33606.

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(Continued on Page 665)

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Excellent opportunity for board certified or board eligible OB/GYN, Pediatric, Internal Medicine and Family Practice physicians to practice within MED-NET (Medical Network of New Mexico), an integrated health care system. Enjoy sunshine, skiing, hiking, fishing and hunting in a Southwestern lifestyle. For further information contact Anne Winter, Director of Professional Development, The St. Joseph Healthcare System, Albuquerque, New Mexico.

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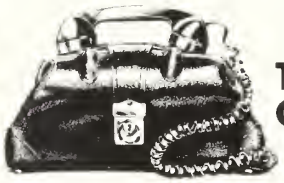
Researching career opportunities takes time that you don't have. And often when you do, no one else is at work to help you. But the new **Practice Opportunity Line** offers an easy, no pressure, confidential way to conduct the search on your own, 24 hours a day. All you have to do is call, follow the prompts and research the openings. Then send a voice mail mini-resume to the opportunities you wish to pursue. It's fast. It's easy. And you're awake anyway.



The Practice Opportunity Line

We're on call for you.

(Continued from Page 664)

PHYSICIANS WANTED

WASHINGTON. Openings for career oriented Emergency Physicians, BC in Emergency or Primary medical specialty. Seattle metropolitan hospital with 54,000 annual visits. Excellent salary in a stable growing group. Contact Maurice Montag in care of Tammie Johnson, 8009 S 180th, Ste 110, Kent, WA 98032; (206) 575-2595.

THINK ABOUT IT!! Arizona needs Primary Care physicians in several underserved areas. From northern plateaus to southern plains, both urban and rural- solo to multispecialty. Great family lifestyle, full benefits, excellent salaries. Write Bill De Long, Catalina Professional Recruiters, PO Box 12650, Tucson, AZ 85732, or call (800) 658-9166.

COASTAL NORTHERN CALIFORNIA. BC/BE FAMILY PRACTITIONER, OB-competent, for nonprofit community clinic in coastal redwood country. Rural university town. Full-time with benefits, $90,000. 1/4 call. NHSL possible. CV to Julie Ohnemus, Northcountry Clinic, 785 18th St, Arcata, CA 95521; (707) 822-2481.

THE VA MEDICAL CENTER, PRESCOTT, ARIZONA is seeking a BC/BE Internist with or without subspecialty. Regular hours. Experience with Holter monitors, treadmill testing, and/or endoscopy desirable but not necessary. Prescott is a lovely area with beautiful surroundings, clean air, pleasant lifestyle, wonderful dry four season climate. Interested physicians may call (602) 445-4860, ext 6640, or send CV to Robert Parsons, MD, Acting Chief, Medical Service, VA Medical Center, Prescott, AZ 86313. An equal opportunity employer.

PHYSICIANS WANTED

OBSTETRICIAN/GYNECOLOGIST
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Nationally renowned multispecialty group seeks to add two OB/GYNs to its satellite clinic network in growing suburbs of Seattle. Join two other physicians in either site and do 12 to 15 deliveries per month. Live in the Evergreen State with incomparable beauty and diverse cultural, educational, and recreational opportunities. Great opportunity for single or married physicians. Compensation commensurate with experience. Excellent benefit package. **For more information call Pat Wall at (800) 462-1857.**

LUSH HAWAII, CALIFORNIA, AND FLORIDA COAST clinics need Family Practitioners, Pediatricians, or Internists, to $120,000. Clear speech Malpractice/benefits/fees paid. OB/GYN, $150-200,000. CV: LAM Associates, Dept W, 444 Hobron Ln, #207H, Honolulu, HI 96815-1229; Pat Lam, (800) 258-4526, 11 am - 9 pm PST.

BC/BE FAMILY PRACTITIONER with interest in OB and a commitment to caring for the underserved, needed to join clinics in Hermiston, Oregon. Diverse cultural influences. Rural setting, abundant recreational opportunities. Competitive salary, Public Health Service loan repayment slots, professional liability, excellent benefit package including vacation up to 32 days per year. Contact Ann Garza, Director of Personnel, or Sylvan Robb, Recruiting Specialist, at (509) 865-5898.

PHYSICIANS WANTED

PEDIATRICIANS–Southern California. Challenging career opportunities for Pediatricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation. Submit CV to J. Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

OB/GYN–Southern California Career opportunities for ambitious Obstetricians desiring private practice. Growing, prestigious, university-affiliated south bay medical center is recruiting BC/BE physicians for expanding solo and group practices. Excellent compensation Submit CV to J Michaels, 2600 Cliff Dr, Newport Beach, CA 92663.

PUGET SOUND–WASHINGTON STATE. Rheumatology independent practice opportunity in Seattle area in a multispecialty clinic with ASC. First year income guarantee with start-up assistance. Attention: Joanne Luttrell, North Kitsap Medical Center, 20696 Bond Rd NE, Poulsbo, WA 98370; (206) 697-4967.

MONTANA, IDAHO, WASHINGTON. Excellent opportunity for lifestyle change. Physicians needed; rural and city locations. Income guarantee and excellent benefit packages. Outdoor recreation plentiful. Call or send CV to FHS, 4656 Utah, Butte, MT 59701; (406) 494-1448.

TWO INVASIVE CARDIOLOGISTS AND FAMILY PHYSICIANS NEEDED. Unique opportunity. Gorgeous California central coast. Partnership within year. Send references/CV to PO Box 220, 395 Del Monte Center, Monterey, CA 93940.

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Reference: 1. Jones PH, et al. Once-daily pravastatin in patients with primary hypercholesterolemia: a dose-response study. *Clin Cardiol.* 1991;14:146-151.

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CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

Active liver disease or unexplained, persistent elevations in liver function tests (see WARNINGS).

Pregnancy and lactation. Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **Pravastatin should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards.** If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.

WARNINGS

Liver Enzymes: HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. Increases of serum transaminase (ALT, AST) values to more than 3 times the upper limit of normal occurring on 2 or more (not necessarily sequential) occasions have been reported in 1.3% of patients treated with pravastatin in the U.S. over an average period of 18 months. These abnormalities were not associated with cholestasis and did not appear to be related to treatment duration. In those patients in whom these abnormalities were believed to be related to pravastatin and who were discontinued from therapy, the transaminase levels usually fell slowly to pretreatment levels. These biochemical findings are usually asymptomatic although worldwide experience indicates that anorexia, weakness, and/or abdominal pain may also be present in rare patients.

As with other lipid-lowering agents, liver function tests should be performed during therapy with pravastatin. Serum aminotransferases, including ALT (SGPT), should be monitored before treatment begins, every six weeks for the first three months, every eight weeks during the remainder of the first year, and periodically thereafter (e.g., at about six-month intervals). Special attention should be given to patients who develop increased transaminase levels. Liver function tests should be repeated to confirm an elevation and subsequently monitored at more frequent intervals. If increases in AST and ALT equal or exceed three times the upper limit of normal and persist, then therapy should be discontinued. Persistence of significant aminotransferase elevations following discontinuation of therapy may warrant consideration of liver biopsy.

Active liver disease or unexplained transaminase elevations are contraindications to the use of pravastatin (see CONTRAINDICATIONS). Caution should be exercised when pravastatin is administered to patients with a history of liver disease or heavy alcohol ingestion (see CLINICAL PHARMACOLOGY: Pharmacokinetics/Metabolism). Such patients should be closely monitored, started at the lower end of the recommended dosing range, and titrated to the desired therapeutic effect.

Skeletal Muscle: Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has been reported with pravastatin and other drugs in this class. Uncomplicated myalgia has also been reported in pravastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal was reported to be possibly due to pravastatin in only one patient in clinical trials (<0.1%). Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **Pravastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. Pravastatin therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma; severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy.**

The risk of myopathy during treatment with lovastatin is increased if therapy with either cyclosporine, gemfibrozil, erythromycin, or niacin is administered concurrently. There is no experience with the use of pravastatin together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with pravastatin together with niacin. One trial of limited size involving combined therapy with pravastatin and gemfibrozil showed a trend toward more frequent CPK elevations and patient withdrawals due to musculoskeletal symptoms in the group receiving combined treatment as compared with the groups receiving placebo, gemfibrozil, or pravastatin monotherapy. Myopathy was not reported in this trial (see PRECAUTIONS: Drug Interactions). One patient developed myopathy when clofibrate was added to a previously well tolerated regimen of pravastatin, the myopathy resolved when clofibrate therapy was stopped and pravastatin treatment continued. **The use of fibrates alone may occasionally be associated with myopathy. The combined use of pravastatin and fibrates should generally be avoided.**

PRECAUTIONS

General: Pravastatin may elevate creatine phosphokinase and transaminase levels (see ADVERSE REACTIONS). This should be considered in the differential diagnosis of chest pain in a patient on therapy with pravastatin.

Homozygous Familial Hypercholesterolemia. Pravastatin has not been evaluated in patients with rare homozygous familial hypercholesterolemia. In this group of patients, it has been reported that HMG-CoA reductase inhibitors are less effective because the patients lack functional LDL receptors.

Renal Insufficiency. A single 20 mg oral dose of pravastatin was administered to 24 patients with varying degrees of renal impairment (as determined by creatinine clearance). No effect was observed on the pharmacokinetics of pravastatin or its 3α-hydroxy isomeric metabolite (SO 31,906). A small increase was seen in mean AUC values and half-life (t1/2) for the inactive enzymatic ring hydroxylation metabolite (SO 31,945). Given this small sample size, the dosage administered, and the degree of individual variability, patients with renal impairment who are receiving pravastatin should be closely monitored.

Information for Patients: Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Drug Interactions: *Immunosuppressive Drugs, Gemfibrozil, Niacin (Nicotinic Acid), Erythromycin.* See WARNINGS: Skeletal Muscle.

Antipyrine. Clearance by the cytochrome P450 system was unaltered by concomitant administration of pravastatin. Since pravastatin does not appear to induce hepatic drug-metabolizing enzymes, it is not expected that any significant interaction of pravastatin with other drugs (e.g., phenytoin, quinidine) metabolized by the cytochrome P450 system will occur.

Cholestyramine/Colestipol. Concomitant administration resulted in an approximately 40 to 50% decrease in the mean AUC of pravastatin. However, when pravastatin was administered 1 hour before or 4 hours after cholestyramine or 1 hour before colestipol and a standard meal, there was no clinically significant decrease in bioavailability or therapeutic effect. (See DOSAGE AND ADMINISTRATION: Concomitant Therapy.)

Warfarin. In a study involving 10 healthy male subjects given pravastatin and warfarin concomitantly for 6 days, bioavailability parameters at steady state for pravastatin (parent compound) were not altered. Pravastatin did not alter the plasma protein-binding of warfarin. Concomitant dosing did increase the AUC and Cmax of warfarin but did not produce any changes in its anticoagulant action (i.e., no increase was seen in mean prothrombin time after 6 days of concomitant therapy). However, bleeding and extreme prolongation of prothrombin time has been reported with another drug in this class. Patients receiving warfarin-type anticoagulants should have their prothrombin times closely monitored when pravastatin is initiated or the dosage of pravastatin is changed.

Cimetidine. The AUC_{0-12hr} for pravastatin when given with cimetidine was not significantly different from the AUC for pravastatin when given alone. A significant difference was observed between the AUC's for pravastatin when given with cimetidine compared to when administered with antacid.

Digoxin. In a crossover trial involving 18 healthy male subjects given pravastatin and digoxin concurrently for 9 days, the bioavailability parameters of digoxin were not affected. The AUC of pravastatin tended to increase, but the overall bioavailability of pravastatin plus its metabolites SO 31,906 and SO 31,945 was not altered.

Gemfibrozil: In a crossover study in 20 healthy male volunteers given concomitant single doses of pravastatin and gemfibrozil, there was a significant decrease in urinary excretion and protein binding of pravastatin. In addition, there was a significant increase in AUC, Cmax, and Tmax for the pravastatin metabolite SO 31,906. Combination therapy with pravastatin and gemfibrozil is generally not recommended.

In interaction studies with *aspirin, antacids* [1 hour prior to PRAVACHOL (pravastatin sodium)], *cimetidine, nicotinic acid,* or *probucol,* no statistically significant differences in bioavailability were seen when PRAVACHOL was administered.

Other Drugs: During clinical trials, no noticeable drug interactions were reported when PRAVACHOL was added to: diuretics, antihypertensives, digitalis, converting-enzyme inhibitors, calcium channel blockers, beta-blockers, or nitroglycerin.

Endocrine Function: HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower circulating cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Results of clinical trials with pravastatin in males and post-menopausal females were inconsistent with regard to possible effects of the drug on basal steroid hormone levels. In a study of 21 males, the mean testosterone response to human chorionic gonadotropin was significantly reduced ($p<0.004$) after 16 weeks of treatment with 40 mg of pravastatin. However, the percentage of patients showing a ≥50% rise in plasma testosterone after human chorionic gonadotropin stimulation did not change significantly after therapy in these patients. The effects of HMG-CoA reductase inhibitors on spermatogenesis and fertility have not been studied in adequate numbers of patients. The effects, if any, of pravastatin on the pituitary-gonadal axis in pre-menopausal females are unknown. Patients treated with pravastatin who display clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should also be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients also receiving other drugs (e.g., ketoconazole, spironolactone, cimetidine) that may diminish the levels or activity of steroid hormones.

CNS Toxicity: CNS vascular lesions, characterized by perivascular hemorrhage and edema and mononuclear cell infiltration of perivascular spaces, were seen in dogs treated with pravastatin at a dose of 25 mg/kg/day, a dose that produced a plasma drug level about 50 times higher than the mean drug level in humans taking 40 mg/day. Similar CNS vascular lesions have been observed with several other drugs in this class.

A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion starting at 60 mg/kg/day, a dose that produced mean plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose (as measured by total enzyme inhibitory activity). This same drug also produced vestibulocochlear Wallerian-like degeneration and retinal ganglion cell chromatolysis in dogs treated for 14 weeks at 180 mg/kg/day, a dose which resulted in a mean plasma drug level similar to that seen with the 60 mg/kg dose.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a 2-year study in rats fed pravastatin at doses of 10, 30, or 100 mg/kg body weight, there was an increased incidence of hepatocellular carcinomas in males at the highest dose ($p<0.01$). Although rats were given up to 125 times the human dose (HD) on a mg/kg body weight basis, their serum drug levels were only 6 to 10 times higher than those measured in humans given 40 mg pravastatin as measured by AUC.

The oral administration of 10, 30, or 100 mg/kg (producing plasma drug levels approximately 0.5 to 5.0 times human drug levels at 40 mg) of pravastatin to mice for 22 months resulted in a statistically significant increase in the incidence of malignant lymphomas in treated females when all treatment groups were pooled and compared to controls ($p<0.05$). The incidence was not dose-related and male mice were not affected.

A chemically similar drug in this class was administered to mice for 72 weeks at 25, 100, and 400 mg/kg body weight, which resulted in mean serum drug levels approximately 3, 15, and 33 times higher than the mean human serum drug concentration (as total inhibitory activity) after a 40 mg oral dose. Liver carcinomas were significantly increased in high-dose females and mid- and high-dose males, with a maximum incidence of 90 percent in males. The incidence of adenomas of the liver was significantly increased in mid- and high-dose females. Drug treatment also significantly increased the incidence of lung adenomas in mid- and high-dose males and females. Adenomas of the eye Harderian gland (a gland of the eye of rodents) were significantly higher in high-dose mice than in controls.

No evidence of mutagenicity was observed *in vitro*, with or without rat-liver metabolic activation, in the following studies: microbial mutagen tests, using mutant strains of *Salmonella typhimurium* or *Escherichia coli*, a forward mutation assay in L5178Y TK +/− mouse lymphoma cells, a chromosomal aberration test in hamster cells, and a gene conversion assay using *Saccharomyces cerevisiae*. In addition, there was no evidence of mutagenicity in either a dominant lethal test in mice or a micronucleus test in mice.

In a study in rats, with daily doses up to 500 mg/kg, pravastatin did not produce any adverse effects on fertility or general reproductive performance. However, in a study with another HMG-CoA reductase inhibitor, there was decreased fertility in male rats treated for 34 weeks at 25 mg/kg body weight, although this effect was not observed in a subsequent fertility study when this same dose was administered for 11 weeks (the entire cycle of spermatogenesis, including epididymal maturation). In rats treated with this same reductase inhibitor at 180 mg/kg/day, seminiferous tubule degeneration (necrosis and loss of spermatogenic epithelium) was observed. Although not seen with pravastatin, two similar drugs in this class caused drug-related testicular atrophy, decreased spermatogenesis, spermatocytic degeneration, and giant cell formation in dogs. The clinical significance of these findings is unclear.

Pregnancy: Pregnancy Category X: See CONTRAINDICATIONS.

Safety in pregnant women has not been established. Pravastatin was not teratogenic in rats at doses up to 1000 mg/kg daily or in rabbits at doses of up to 50 mg/kg daily. These doses resulted in 20x (rabbit) or 240x (rat) the human exposure based on surface area ($mg/meter^2$). However, in studies with another HMG-CoA reductase inhibitor, skeletal malformations were observed in rats and mice. PRAVACHOL (pravastatin sodium) should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking PRAVACHOL, it should be discontinued and the patient advised again as to the potential hazards to the fetus.

Nursing Mothers: A small amount of pravastatin is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, women taking PRAVACHOL should not nurse (see CONTRAINDICATIONS).

Pediatric Use: Safety and effectiveness in individuals less than 18 years old have not been established. Hence, treatment in patients less than 18 years old is not recommended at this time. (See also PRECAUTIONS: **General**.)

ADVERSE REACTIONS

Pravastatin is generally well tolerated, adverse reactions have usually been mild and transient. In 4-month long placebo-controlled trials, 1.7% of pravastatin-treated patients and 1.2% of placebo-treated patients were discontinued from treatment because of adverse experiences attributed to study drug therapy, this difference was not statistically significant. In long-term studies, the most common reasons for discontinuation were asymptomatic serum transaminase increases and mild, non-specific gastrointestinal complaints. During clinical trials the overall incidence of adverse events in the elderly was not different from the incidence observed in younger patients.

Adverse Clinical Events: All adverse clinical events (regardless of attribution) reported in more than 2% of pravastatin-treated patients in the placebo-controlled trials are identified in the table below, also shown are the percentages of patients in whom these medical events were believed to be related or possibly related to the drug.

	All Events %		Events Attributed to Study Drug %	
Body System/Event	Pravastatin (N = 900)	Placebo (N = 411)	Pravastatin (N = 900)	Placebo (N = 411)
Cardiovascular				
Cardiac Chest Pain	4.0	3.4	0.1	0.0
Dermatologic				
Rash	4.0*	1.1	1.3	0.9
Gastrointestinal				
Nausea/Vomiting	7.3	7.1	2.9	3.4
Diarrhea	6.2	5.6	2.0	1.9
Abdominal Pain	5.4	6.9	2.0	3.9
Constipation	4.0	7.1	2.4	5.1
Flatulence	3.3	3.6	2.7	3.4
Heartburn	2.9	1.9	2.0	0.7
General				
Fatigue	3.8	3.4	1.9	1.0
Chest Pain	3.7	1.9	0.3	0.2
Influenza	2.4*	0.7	0.0	0.0
Musculoskeletal				
Localized Pain	10.0	9.0	1.4	1.5
Myalgia	2.7	1.0	0.6	0.0
Nervous System				
Headache	6.2	3.9	1.7*	0.2
Dizziness	3.3	3.2	1.0	0.5
Renal/Genitourinary				
Urinary Abnormality	2.4	2.9	0.7	1.2
Respiratory				
Common Cold	7.0	6.3	0.0	0.0
Rhinitis	4.0	4.1	0.1	0.0
Cough	2.6	1.7	0.1	0.0

*Statistically significantly different from placebo.

The following effects have been reported with drugs in this class:

Skeletal: myopathy, rhabdomyolysis.

Neurological: dysfunction of certain cranial nerves (including alteration of taste, impairment of extra-ocular movement, facial paresis), tremor, vertigo, memory loss, paresthesia, peripheral neuropathy, peripheral nerve palsy.

Hypersensitivity Reactions: An apparent hypersensitivity syndrome has been reported rarely which has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome.

Gastrointestinal: pancreatitis, hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma, anorexia, vomiting.

Reproductive: gynecomastia, loss of libido, erectile dysfunction.

Eye: progression of cataracts (lens opacities), ophthalmoplegia.

Laboratory Test Abnormalities: Increases in serum transaminase (ALT, AST) values and CPK have been observed (see WARNINGS).

Transient, asymptomatic eosinophilia has been reported. Eosinophil counts usually returned to normal despite continued therapy. Anemia, thrombocytopenia, and leukopenia have been reported with other HMG-CoA reductase inhibitors.

Concomitant Therapy: Pravastatin has been administered concurrently with cholestyramine, colestipol, nicotinic acid, probucol and gemfibrozil. Preliminary data suggest that the addition of either probucol or gemfibrozil to therapy with lovastatin or pravastatin is **not** associated with greater reduction in LDL-cholesterol than that achieved with lovastatin or pravastatin alone. No adverse reactions unique to the combination or in addition to those previously reported for each drug alone have been reported. Myopathy and rhabdomyolysis (with or without acute renal failure) have been reported when another HMG-CoA reductase inhibitor was used in combination with immunosuppressive drugs, gemfibrozil, erythromycin, or lipid-lowering doses of nicotinic acid. Concomitant therapy with HMG-CoA reductase inhibitors and these agents is generally not recommended. (See WARNINGS: **Skeletal Muscle** and PRECAUTIONS: **Drug Interactions.**)

OVERDOSAGE

There have been no reports of overdoses with pravastatin.

Should an accidental overdose occur, treat symptomatically and institute supportive measures as required.

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Bristol-Myers Squibb Company

THE PRAVACHOL® DIRECTION IN LIPID MANAGEMENT

Effective lipid management doesn't have to be tough

- Improves key lipids — significant reduction in LDL-C[1]
- Excellent safety profile
- Easy for patients — once-daily dosing, well tolerated
- Usual dose: 20 mg once daily at bedtime, with or without food

PRAVACHOL®

pravastatin sodium 20 mg tablets

PRAVACHOL is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia (Types IIa and IIb) when the response to diet alone has not been adequate.

Active liver disease or unexplained transaminase elevations, pregnancy and lactation are contraindications to the use of pravastatin sodium.

Please see CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the brief summary of prescribing information on the adjacent page.

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